

INTRODUCTION

Thalassemia major is a rare, complex disease. It is unrealistic to expect that a practitioner with a small number of patients with thalassemia could become expert in the care of patients with this disease. All patients should be referred to Comprehensive Thalassemia Centers for evaluation and development of comprehensive management plans. A similar model of care has been successful for patients with a more common hemoglobinopathy: sickle cell anemia. The following guidelines were developed as a consequence of the Thalassemia Providers Conference held in Pasadena California on June 9, 2000. These guidelines primarily address the management of thalassemia patients who are being transfused. There are other approaches for the management of thalassemia intermedia syndromes, which do not include regular transfusions.

Transfusion is the mainstay of the care of individuals with thalassemia major. The purpose of transfusion is twofold; to improve the anemia and to suppress the ineffective erythropoiesis. Chronic transfusions prevent most of the serious growth, skeletal, and neurological complications of thalassemia major. However, once started, the transfusion-related complications become a major source of morbidity. Standards must be developed and maintained to ensure a safe and rational approach to the use of blood transfusions in the management of these rare disorders.

Patients with heterozygous β thalassemia, E- β^0 -thalassemia, hemoglobin H disease and Hemoglobin-H-Constant Spring often have a thalassemia intermedia phenotype and do not necessarily require chronic transfusions. In fact, it is best if transfusion can be avoided. The decision to start transfusion is often difficult, particularly in the thalassemia-intermedia syndromes. In general, patients with hemoglobin less than 7 gm/dl will likely require chronic transfusion. However, the institution of chronic transfusion is rarely emergent.

The decision to start transfusions is based on inability to compensate for the low hemoglobin (signs of increased cardiac effort, tachycardia, sweating, poor feeding, and poor growth), or less commonly, due to increasing symptoms of ineffective erythropoiesis (bone changes, massive splenomegaly). The decision to institute chronic transfusions should not be based exclusively on the presence of anemia.

I. DIAGNOSIS OF THALASSEMIA

Prior to consideration of transfusion therapy, it is critical to confirm that the patient has thalassemia major and to eliminate other concomitant causes of anemia. Once transfusion has

been started, it is more difficult to establish the correct diagnosis and almost impossible to diagnose thalassemia-intermedia. Patients with thalassemia intermedia may have exaggerated anemia because of concomitant iron or folic acid deficiency. Correcting these deficiencies may raise the hemoglobin enough to obviate the need for transfusion. Patients with thalassemia trait and iron deficiency can masquerade as thalassemia intermedia.

- In addition to complete blood count, hemoglobin electrophoresis is the first diagnostic test. Fractions of hemoglobin A, A₂, F, H, E and other variants are measured.
- Measure serum ferritin, total iron binding capacity, serum iron, and red cell folate. Consider a brief therapeutic trial of iron (6 mg/kg/day for 4 to 8 weeks) and folic acid (1 mg /day) if indicated by the laboratory examinations.
- Both β and α globin gene mapping should be determined on all patients to confirm the diagnosis and determine the presence of co-inherited α globin gene defects that may affect prognosis and management.

II. TRANSFUSION THERAPY

A. GENERAL RECOMMENDATIONS AT INITIATION OF REGULAR TRANSFUSIONS:

Evaluation prior to starting transfusions:

- Red cell antigen phenotype to identify the complete minor antigen typing.

- CMV serology testing: IgM in infants and IgG in older children who may have future possibility of bone marrow transplantation (BMT). Candidate patients for BMT are transfused with leukodepleted blood products. If possible, CMV-negative blood products should be used.
- Perform serologic testing for HIV, hepatitis A, B, and C, and liver function testing (ALT, AST, and fractionated bilirubin) to provide baseline prior to initiation of transfusion.
- Immunize all patients who do not have serologic evidence of infection or immunity for hepatitis B prior to transfusion. Hepatitis A immunization should be given as well.
- HLA type all full siblings of patients with transfusion-dependent thalassemia. Note that parents who are HLA identical to their children have been identified in families from certain geographic regions.
- If the patient has already been started on transfusions and the history of the indication for transfusion is unclear, reassess need for chronic transfusion by discontinuing transfusions. Reinstate transfusion if the hemoglobin falls to < 6.5 g/dl, in the face of no other nutritional deficiencies accounting for the anemia.

B. TRANSFUSION ADMINISTRATION AND MONITORING:

- Schedule transfusions at three to four week intervals to maintain hemoglobin level greater than or equal to 9-9.5 gm/dl prior to the next transfusion.
- Evaluate hemoglobin prior to each transfusion. If the pre-transfusion hemoglobin is less than 9.0 gm/dl, the patient may need more frequent (every two to three weeks) transfusions or increased volume of transfusion.
- Mean hemoglobin for chronically transfused individuals should be 12 to 12.5 gm/dl, and the hemoglobin post transfusion should not exceed 15 gm/dl.
- Hemoglobin levels and reticulocyte counts may not adequately reflect suppression of ineffective erythropoiesis. Serum transferrin receptor (stfr) levels reflect level of ineffective erythropoiesis more adequately and are being used in some centers to monitor efficacy of chronic transfusions in thalassemic patients.
- Assess spleen size at each visit, splenomegaly could account for increased blood requirement.
- Evaluate total transfusion requirement every 6 months: Calculate all blood given to the patient (total cc's) and divided by an average weight over the past 6 months (cc / kg / year). If transfusion requirement is greater than 200 cc / kg / year, the cause for such a high transfusion requirement should be explored.
- In the face of marked splenomegaly or other evidence of significant hypersplenism (leukopenia, thrombocytopenia) splenic embolization, splenectomy or partial splenectomy may be considered.

C. ALLOANTIBODIES AND AUTOANTIBODIES:

- Autoimmunization or alloimmunization should be considered if the hemoglobin is less than 9.0-9.5 gm/dl or is significantly less than usual for the particular patient prior to the transfusion on two occasions. Hemoglobin level and direct and indirect Coombs test should be determined 24 to 72 hours after the transfusion to determine whether the projected increase in hemoglobin has been attained and maintained.

- If an autoantibody or/and alloantibody is detected, the specific antibodies causing the transfusion reaction should be determined by the blood bank or by a reference laboratory.
- The management of antibodies in patients who require chronic transfusions and develop antibodies is not straightforward. The use of blood matched by extended antigen is usually indicated. Other treatment modalities, as steroids or immunosuppressive agents may be considered as well.
- Generally, the use of phenotypically matched blood products, at minor antigens, from the beginning of chronic transfusion, can prevent most cases of alloimmunization.

D. SPLENECTOMY AS MANAGEMENT OF TRANSFUSION REQUIREMENT:

- Splenectomy is generally not recommended for thalassemia patients because of the risk of the complications listed below. However, in selected cases splenectomy (total or partial) may be indicated.
- Splenectomy is associated with significant risk of serious short and long term complications: Infectious, pulmonary, hepatic, and thrombotic.

In case splenectomy is found to still be indicated:

- Pre splenectomy: Obtain pneumococcal IgG titers. If the titers are inadequate, immunize to maximize coverage of all serotypes (7-valent conjugate vaccine recommended in children under five years (Prevnar), 23 valent (Pneumovax) as a booster at five years of age or later). Reimmunize patients with inadequate IgG responses.
- Post splenectomy: Monitor the platelet count and treat with an anti-platelet aggregate (low dose Aspirin) if platelet count is 1×10^6 or greater.
- Hemoglobin H-Constant Spring patients may have increased thrombotic events post-splenectomy and may require long-term anti-coagulant therapy. For the immediate post-surgical course treat with low molecular heparin, and continue with an oral anti coagulant or anti platelet aggregate.
- Consider chronic low dose anticoagulation (coumadin) or anti-platelet agent (aspirin) in older splenectomized patients reduce the risk of pulmonary thrombotic events and pulmonary hypertension.
- All post splenectomy thalassemia patients require treatment with prophylactic penicillin. Intensive family education should be provided, regarding the need for immediate medical attention if the patient develops high fever.

III. IRON OVERLOAD AND CHELATION THERAPY

Iron overload is the major cause of morbidity for patients on chronic transfusions. Non-transfused patients with thalassemia intermedia have increased intestinal absorption of dietary iron as well and can have significant complications from iron overload as well. Major morbidity and mortality can result from iron load: Liver dysfunction and failure, pan-endocrine failure, heart failure and fatal cardiac arrhythmias, which constitute the main concerns in poorly chelated patients.

Monitoring of iron overload: Serum ferritin is routinely available, but often results in inaccuracy in determination of iron loading. At the current time, direct measurement of hepatic iron, by liver biopsy or by a super-conducting quantum interference device (SQUID), is the most accurate method to determine iron loading.

A. INITIATION OF CHELATION:

- A liver biopsy measurement of hepatic iron should be performed within the first two years of transfusion therapy. If a liver biopsy cannot be performed, serum ferritin can be used as a marker of iron.
- Chelation should be considered after one to two years of transfusion therapy, when the serum ferritin is greater than 1000 ng/dL, or when the hepatic iron is approximately 7 mg /gram dry weight.
- Starting life-long transfusions and chelation has a significant impact on the patient and family. Compliance with this therapy is probably the most important factor in reducing the morbidity on chronic transfusion therapy. A protocol should be established for

initiation and phasing-in of desferrioxamine (Desferrioxamine) therapy. Effective nursing, child life services, and psychological support services are needed in order to encourage compliance and a smooth transition to this life-long therapy.

B. TREATMENT WITH DESFERRIOXAMINE (DESFERAL):

Desferrioxamine is only routinely available drug for the removal of excess iron in chronically transfused patients. It is an effective chelator when taken properly, as described below. Generally, iron is removed much more efficiently when desferrioxamine is infused over a longer period of time. The dose depends somewhat upon the age of the patient and the degree of iron overload. Side effects of desferrioxamine are greater at lower levels of iron loading and in children under two to three years of age. The mainstay of therapy is sub-coetaneous (SQ) desferrioxamine, slowly infused approximately six nights a week.

- Subcutaneous desferrioxamine should be administered at 30 to 50 mg / kg/ for 8 to 12 hours five to seven days per week. Starting at a lower frequency may help the family adapt to and accept the new therapy. A small gauge needle in the thigh or abdomen is usually used. It is important that the needle be long enough to go through the dermis. Intradermal infusion is painful and results in blisters, swelling and reactions. The sites should be rotated to prevent reaction and fat necrosis. (See following section for treatment suggestions of local reactions).
- Additional intravenous (IV) desferrioxamine can be given with each transfusion at a dose of 35 to 50 mg/kg to run at the length of the transfusion (or longer) at a maximum of 15 mg/kg/hour. The dose varies, depending on the patient's age and the degree of iron loading.
- To improve compliance, the major cause of therapeutic failure, creativity in methods to minimize impact on life style and ample support from nursing, child-life and social workers are critical in the success of treatment.
- Oral iron chelators: The efficacy and toxicity of Deferiprone (L1), the only oral chelator studies in large clinical trials, are controversial. This oral chelator is not yet FDA approved in th U.S.
- Other measures for reducing the iron level:
 - a) Ascorbic acid (Vitamin C) is started after the initial month of therapy, 2-mg/kg/day (100 to 250 mg) orally with each infusion taken after infusion has been initiated. Patients should be cautioned against excessive ascorbate intake while desferrioxamine is **not** being infused. Ascorbate releases iron and has been associated with increased cardiac damage when taken in the absence of an iron chelator.
 - b) Low iron diet, as well as tea drinking with meals, are encouraged for all transfused patients.

1. Patients with Significant Iron Overload:

An aggressive chelation regimen is recommended when liver iron > 15 mg/gram dry weight and ferritin is over 2500-3000ng/ml.

A high dose of desferrioxamine is recommended. Intensification of treatment can be done by administration of continuous intravenous desferrioxamine (via a central intravenous line if possible) in the hospital or in the outpatient/day unit. A minimum of 72 hours one to two times a month in addition to regular use of subcutaneous desferrioxamine is

recommended. Intravenous treatment is given at 50-100 mg/Kg/day (maximum dose 6 grams/day). This regimen should be continued until the ferritin is less than 2000 ng/ml on two consecutive occasions. Alternative regimens: Daily intravenous administration of Desferrioxamine, continuous Desferrioxamine via “percutaneous line” or indwelling venous access device. In all such treatment high dose continuous treatments require carefully monitoring for signs of toxicity.

2. Assessment and Monitoring of Iron Overload:

- Determination of liver iron by biopsy is recommended prior to initiation of desferrioxamine therapy as well as every 12 to 24 months (or as clinically indicated). Though not routinely available, liver iron can be also determined by ferritometry (SQUID).
- Evaluation of liver iron tissue biopsy: Part of the specimen is imbedded in paraffin for standard histology and part is sent to a reference lab for direct measurement of iron. Absence of iron contamination during fixation and imbedding is critical for accurate quantitative iron measurement. Note that estimation of iron content by histological staining of the biopsy is not accurate or acceptable for monitoring of iron overload.
- Evaluate ferritin level quarterly. Average ferritin levels should be less than 1000 ng/ml. While ferritin alone is a poor indicator of compliance, in conjunction with liver biopsy, following trends can be useful.
- Persistent ferritin levels greater than 2500 ng/ml (in the absence of hepatitis or other inflammatory process) and hepatic iron greater than 7 mg/gm are considered dangerously elevated. Such findings should prompt evaluation of compliance, chelation protocol, dose Desferrioxamine, serum vitamin C, annual and semiannual transfusion requirement, as well as hepatitis status, liver function and liver biopsy results. The most common reason for failure to respond to treatment is non-compliance. This requires assessment and intervention by the team psychologist and nurse.
- Liver iron greater than 15-mg/g dry weight implies great risk for cardiac complications of hemochromatosis. A more aggressive chelation program is immediately indicated. Initiation of intravenous desferrioxamine in addition to regular use of subcutaneous desferrioxamine is strongly recommended. (see details above. Continuous intravenous desferrioxamine infusions are usually reserved for patients who have cardiac failure or inability to use subcutaneous desferrioxamine or have toxic levels of hepatic iron). High dose continuous desferrioxamine must be monitored carefully to prevent desferrioxamine of toxicity.
- The importance of liver biopsy must again be stressed. Patients can have a ferritin level in the 500 to 800 ng/ml range and have liver iron levels over 35-mg/gm dry weight.
- Parents and patients should be aware of the results of these tests and understand their implications; Compliance with desferrioxamine should be assessed by patient and family report and by the physical examination of infusion sites.

- If compliance and other causes for iron overload have been addressed, and there is questionable efficacy of chelation, quantitative urinary iron levels can be obtained to determine the efficacy of chelation. These studies are not routinely performed.

The following criteria are used in evaluation of hemosiderosis (Iron Chelating Therapy and the Treatment of Thalassemia; Olivieri and Brittenham Blood 89:3,1997,739-761):

TABLE I

CHRONIC IRON OVERLOAD		
	TOXICITY	HEPATIC IRON
Desferrioxamine Toxicity	Hearing Loss	< 3 mg/g dry wt
	Blindness	
	Growth Failure	
Optimal Hepatic Iron Level		4 to 7.5 mg/g dry wt
Risk of Endocrine Complications	Diabetes Mellitus	7.5 to 15mg/g dry wt
	Hypogonadism	
	Hypoparathyroidism	
	Cirrhosis	> 10 mg / g dry weight
Risk of Cardiovascular Complications	Dysrhythmia	> 15 mg/g dry wt.
	Cardiomyopathy	

4. Assessment of Desferrioxamine Side Effects and Toxicity:

The primary signs of desferrioxamine toxicity are hearing loss, temporary loss of sight, cataracts, renal dysfunction, growth failure, and symptoms related to iron deficiency. The following should be routinely monitored.

Audiology

- Baseline formal audiology prior to starting desferrioxamine.
- Inquire about hearing problems at each monthly visit: history of difficulty hearing or of tinnitus, physical exam of tympanic membranes, perform hearing testing with a tuning fork every 6 months. If there is any abnormality, formal audiology testing should be done.
- Perform a screening test in clinic every 6 months.
- Refer to a formal audiogram assessment every 12 months, or more often if the patient is unable to undergo a screening test in clinic.
- If there is new onset of hearing loss or tinnitus, desferrioxamine should be stopped and the audiogram repeated. The testing should be confirmed within a month. Desferrioxamine can be restarted if the hearing changes have improved. Re-evaluation of iron status may be necessary.

Ophthalmology

- Inquire about decreased visual acuity at each visit. Perform a vision screen if problems are reported.
- Annual evaluation by an ophthalmologist should be performed to rule out cataracts, decreased acuity, night blindness, and decreased visual fields.
- Reevaluation of desferrioxamine dose should be done if any ophthalmologic abnormalities are found.

Renal

- Creatinine and BUN with the serum chemistry (every 3 months)

Growth

- Evaluate for evidence of growth delay. Record monthly routine height and weight. Calculate annually growth velocity.
- Measure sitting height every six months to assess truncal shorting.
- Tibial and spine radiographs are evaluated for evidence of metaphyseal cartilaginous dysplasia in younger patients with evidence of growth delay.

Local and Allergic Reactions

- Local reactions at injection site that are urticarial in nature will usually respond to dilution of the desferrioxamine by increasing the diluent by 25 to 30%. Hydrocortisone should be used only in severe cases and under the direction of the consulting hematologist. . In some cases, treatment with antihistamines may be helpful.

- Severe life-threatening allergic reactions can occur. Patients who report anaphylactic type symptoms should be observed and challenged. Desensitization protocols have been used successfully in some patients. When desensitization has been accomplished, it is critical that the patient does not stop the medication, as it may necessitate reinstitution of the entire desensitization process.

Over Chelation

- Persistent low serum ferritin levels (<500 ng/ml) in face of regular chelation are not optimal due to the increased toxicity of desferrioxamine at low levels of total body iron. The chelation program should be modified (desferrioxamine at 25 mg/kg/dose or less) and liver biopsy results evaluated. Zinc, copper, selenium and ionized calcium levels should be examined as other indicators and concerning findings of desferrioxamine toxicity.

IV. LIVER DISEASE

Liver toxicity can occur as a direct consequence of iron toxicity and/or from transfusion-acquired hepatitis. Liver function and hepatitis serology must be routinely screened in thalassemia patients on chronic transfusion as described below:

A. SCREENING FOR HEPATIC DYSFUNCTION:

- Annual hepatitis B surface antibody, surface antigen, core antibody.

- Annual hepatitis C antibody. If the hepatitis C antibody screen becomes positive, PCR for hepatitis C should be measured.
- Every three months Bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase.
- If the ALT is elevated, it should be repeated in two weeks. If the ALT remains elevated at 2 week or if it is intermittently elevated over a period of three months, a complete evaluation for causes of hepatitis should be performed. Suggested evaluation should include the following:
 1. PT, PTT, albumin, Albumin/globulin ratio.
 2. Hepatitis A IgM. (If not previously positive or known to be immune).
 3. Hepatitis B e antigen and antibody, and hepatitis B DNA quantitation by Branched DNA assay if the hepatitis B surface antigen is reactive (positive) or if hepatitis B core antibody is positive in the absence of hepatitis B surface antigen and antibody.
 4. Hepatitis C antibody. If the antibody screen is positive, viral load should be measured by quantitative PCR.
 5. CMV titers (IgG, IgM), CMV PCR and/or urine culture for CMV.
 6. EBV titers. (PCR for reactivation).
 7. If PCR is positive for hepatitis C, a baseline liver biopsy should be considered to evaluate severity of disease and need for therapy.
 8. Evaluate for autoimmune hepatitis, biliary obstruction, metabolic disease, toxic hepatitis.

B. MONITORING OF PATIENTS WITH DOCUMENTED HEPATITIS OR HEPATIC DYSFUNCTION:

Once hepatic dysfunction has been documented, gastroenterological consultation is critical. The combination of hepatitis and iron overload increases the risk of liver damage. Rapid removal of iron and treatment of viral hepatitis is critical for preserving liver function.

- All patients with hepatitis should be followed by liver biopsy.
- Patients over the age of 18 years who have hepatitis B or C are monitored for hepatocellular carcinoma with alfa fetoprotein and hepatic ultrasound evaluations biannually. This is particularly important if there is evidence of cirrhosis on biopsy.
- Treatment of hepatitis C should be monitored by biopsy using the standardized pathology grading (inflammation) and staging (fibrosis) system: Ludwig J Gastroenterology, 1993; 105:274-278 and Desmet VJ, et. al. Hepatology 1994; 19: 1513-1520.
- Early alfa interferon therapy is recommended for newly acquired infection with hepatitis C.
- Elevated transaminases and liver biopsy results showing stage 2/4 fibrosis as well as stage 2/4 inflammation are indications for treatment.

C. EVALUATION AND TREATMENT FOR HEPATITIS C:

- The decision of whether to recommend treatment of established hepatitis C depends on clinical status, severity of fibrosis (> stage 2/4) and inflammation (> stage 2/4).
- Treatment consists of Interferon alfa, given as a subcutaneous injection three times a week, and oral Ribavirin.
- Pegylated (PEG) interferon alfa may be more effective than the combination of standard interferon alfa and ribavirin (clinical studies in progress).
- Treatment with alfa interferon has significant side-effects and therefore requires monitoring, including:
 - CBC-look for neutropenia, thrombocytopenia.
 - Evidence for hypothyroidism (anti-thyroid peroxidase antibody titer predicts complications of hypothyroidism).
 - Retinal changes.
 - Psychological profile, as depression is common.
- Liver enzymes and hepatitis C PCR, should be monitored for response to treatment.
- Addition of ribavirin ((Rebetron, a combination of interferon alfa and ribavirin)) for patients not responding to alfa interferon or relapsing after initial response requires close monitoring of the hemoglobin because of increased risk of hemolysis. Patients on ribavirin require increased transfusions to avoid complications related to rapidly worsening anemia, particularly cardiac events. An increase chelation is frequently required with increases in blood requirement.

D. EVALUATION AND TREATMENT FOR HEPATITIS B:

- The decision of whether to recommend treatment of established hepatitis B depends on clinical status. Patients with indices of active viral replication (HbeAg and HBV DNA) and of liver injury (elevated transaminases and active hepatitis on biopsy) are candidates for therapy.
- Two drugs are FDA approved for use in adults and children: Alfa interferon for compensated liver disease and lamivudine (Epivir-HBV) for compensated or decompensated liver disease.
- Liver biopsy should be obtained before initiating treatment
- Low HBV DNA (<200 pg/ml) and high baseline ALT (>5x ULN) are associated with improved response for both medications. Results show loss of HbeAg and DNA in approximately 25 to 35 % at one year of therapy with either lamivudine or alfa interferon.
- Alfa interferon has a significant side effect profile as described under the hepatitis C section.

- Lamivudine has the advantage of oral administration and a less significant side effect profile.

Lamivudine side effects include:

- Headache, fever, abdominal discomfort, myalgia.
- Lactic acidosis and steatohepatitis, are rare but can be fatal.
- Doses should be adjusted based on creatinine-clearance, as it is primarily renal excreted.
- Development of non-replicating mutants, the rate increases with extension of therapy.
- Treatment in the presence of unrecognized HIV, favors early development of viral resistance.

V. ENDOCRINE DYSFUNCTION

Endocrine dysfunction due to iron deposition and toxicity to the endocrine tissue, is a common complication of iron overload, causing significant morbidity. Gonadal failure, sterility, and growth failure are common, as well as osteopenia and osteoporosis. Diabetes mellitus may develop as well in patients with iron overload.

A. ROUTINE ENDOCRINE SCREENING:

- Accurate height and weight are measured at each visit. Evaluate growth on ethnically adjusted charts. Sitting height is measured semiannually.
- Annual endocrinologic consultation and screening should be started at five years of age, after three years of transfusions, or as otherwise clinically indicated. The following tests are recommended annually or semiannually:
 1. TSH and free T4.
 2. Cortrosyn stimulation test (can be done every 2 years).
 3. Parathyroid hormone.
 4. Serum calcium, ionized calcium and vitamin D.

5. Fasting glucose semiannually.
6. Oral glucose tolerance testing as indicated by fasting glucose (see following section).
7. IGF-1 and IGF BP-3, for screening for growth hormone deficiency.
8. Bone Density.
9. Trace Elements: zinc, copper, and selenium.

B. SPECIFIC ENDOCRINOPATHIES: TESTING AND EVALUATION:

1. Diabetes Mellitus

- A two-hour oral glucose tolerance testing (OGTT) should be performed at ten, twelve, fourteen and sixteen years of age. The OGTT should be performed annually thereafter.
- If fasting serum glucose is > 110 mg/dl, OGTT is indicated.
- Fasting glucose >126 mg/dl is diagnostic of diabetes mellitus.
- OGTT serum glucose at 2 hours only; > 200 mg/dl is diagnostic of diabetes mellitus.
- OGTT serum glucose at 2 hours > 140 < 200 mg/dl indicates glucose intolerance.
- The patient should be referred to endocrinology for management of diabetes mellitus or glucose intolerance.
- Review and intensify patients' chelation therapy, if diagnosed with glucose intolerance.

2. Osteoporosis

- Initial bone density by Dual-energy X-ray absorptiometry (DEXA) or other accepted methods of measurement should be performed at 8 years for girls and for boys, and annually thereafter. The same method of bone density measurement should be used for each evaluation. There is significant inter-method variability in bone density measures. Therefore, different manufacturers of instruments or methods of assay are not acceptable for monitoring of a single patient over time.
- The absolute value of bone density varies but the accepted definitions are:
 1. Bone density > 1.5 SD below the mean is diagnostic of osteopenia.
 2. Bone density > 2.5 SD below the mean is diagnostic of osteoporosis.
- Annual evaluation of calcium metabolism and parathyroid function: Patients' diet, 25-hydroxy vitamin D, PTH, and serum calcium should be measured. If the patient is achieved puberty or post is pubertal, FSH, LH, testosterone or estrogen should be examined.
- Supplement with calcium 1200 mg/day starting at age 12 years.
- Follow nutritional status and adequate vitamin levels. Supplement with vitamin D 400 units/day for patients with low levels or those at high risk to develop vitamin deficiency.

- For patients with established osteoporosis (DEXA score of >2.5 standard deviations) treatment with bisphosphonates should be considered.
- Endocrine referral is recommended for hormone replacement (estrogen for females, testosterone for males), calcium supplementation, exercise program, and consideration of bisphosphonates.

3. Growth Hormone Deficiency

- Endocrine evaluation is required if there is fall-off on growth curve, height < 5%, or poor growth velocity for age. The evaluation should include:
 1. Dietary assessment by a registered dietitian.
 2. Laboratory tests: Serum Ca, PO₄, albumin, UA, urine culture T₄, TSH and IGF-1, IGF BP-3.
 3. Bone age assessment.
- Low IGF-1 or IGF BP-3 requires investigation by growth hormone provocative testing.
- Referral to endocrinologist for determination and treatment of growth hormone deficiency.
- Early diagnosis, for successful treatment before completion of puberty is recommended.

4. Hypogonadism

- Tanner staging should be determined every 6 months.
- Girls without evidence of advancing pubertal stage by 12 years and boys by 14 years require screening with LH-ICMA, FSH and estradiol levels. Obtain bone age films, if not yet done.
- Elevated FSH and LH-ICMA suggests primary hypogonadism. Low for age FSH and LH-ICMA suspect secondary or tertiary hypogonadism.
- If LH-ICMA and/or FSH are abnormal perform GNRH stimulation. Consider performing at age 12 years in girls and 14 years in boys, then annually as clinically indicated. (This should be done prior to the blood transfusion on a different visit from the OGTT).
- Testosterone levels should be checked annually in males starting in early adolescent years (approximately 12 years old)
- If testosterone level is low, obtain endocrine consultation and start monthly testosterone treatment. The starting dose is usually 100–150 mg given monthly as an IM shot.
- Testosterone dose needs to be adjusted periodically for patients' age and pubertal status as well as for sexually active men.
- Estrogen replacement is recommended for amenorrheic adolescent girls and adult women, Premarin at a low dose (0.0375 micrograms/day for 6 months). Dose is advanced after 6 months to for additional 6-12 months. Afterwards an oral contraceptive pill replaces Premarin.
- Gynecological consultation is recommended in women for estrogen therapy and fertility evaluation.

5. Hypothyroidism

- TSH and free T4 should be measured at age 5 years or after three years of transfusion.
- Elevated TSH, depressed T4 suggests primary hypothyroidism. Depressed TSH, depressed T4 suggests secondary or tertiary hypothyroidism
- Refer to endocrinology and start replacement therapy as indicated.

6. Hypoparathyroidism

- Parathyroid status should be evaluated annually with serum ionized calcium, parathyroid hormone, and 25-hydroxy vitamin D screening.
- A normal PTH with decreased calcium; or a decreased PTH with normal calcium is diagnostic of hypoparathyroidism
- Refer to endocrinology and start therapy with a vitamin D (use an activated 1,25 OH Vit D product) and calcium.

7. Adrenal Insufficiency

- Adrenal status is screened biannually, beginning at age 5 years using ACTH stimulation test. Cortrosyn 1 microgram intravenously is given and cortisol levels are measured 30 and 60 minutes after dosing. A cortisol response of < 17 mg/dl is diagnostic of adrenal insufficiency.
- Patients with abnormal screening are referred to endocrinology for further evaluation and replacement therapy.

VI. CARDIAC DYSFUNCTION

Cardiac disease is the major cause of death in patients with iron overload. It is difficult to predict and measure in the myocardium. However, the risk for cardiomyopathy, arrhythmias and heart failure correlates with hepatic iron levels (see table I). Myocarditis is more common than in the general population and can result in severe morbidity and mortality in this population.

A. CARDIAC EVALUATION:

- Cardiac evaluation with a baseline ECHO cardiogram prior to initiation of transfusion.
- Baseline ECG to monitor for ventricular hypertrophy and rhythm abnormalities.
- Cardiac history (palpitations, irregular heart rate, chest pain, dyspnea, exercise intolerance, nocturnal cough, orthopnea, dependent edema, unexplained fevers) and exam (systemic or pulmonary venous congestion, gallop, edema) should be performed every month. Any positive history of cardiac dysfunction requires evaluation by a cardiologist.
- For patients <12 years old obtain a cardiac ECHO every other year unless clinically indicated.
- For patients > 12 years old obtain a cardiac ECHO every year.
- ECG and a Holter monitor approximately every 2 years until the age of 12 years, and then yearly or as clinically indicated.
- Abnormalities found in this screening require referral to a cardiologist.
- Myocarditis is more common in thalassemia than the general population and should be entertained as a diagnosis in acute decompensation.
- Cardiac findings require assessment of hemosiderosis by liver biopsy and intensification of chelation, surveillance and treatment by cardiology.

B. ECHOCARDIOGRAPHY STANDARDS:

The following parameters should be included in an echocardiographic evaluation:

- M-mode: LV end diastolic and systolic dimensions, wall thickness, LV mass and wall stress, shorting fraction, corrected mean velocity of circumferential shorting.
- Pulse Doppler for mitral inflow peak velocities (E and A), mitral deceleration time and EF slope.

- Color and continuous wave Doppler: severity and velocity of tricuspid and pulmonic regurgitant jets (estimation of RV and pulmonary artery pressures).

Other modalities to determine degree of cardiac dysfunction, not in routine use:

- Stress Assessment of Cardiac Function with cardiac ECHO: Loss of contractility with exercise or dobutamine infusion precedes reduced resting shorting fraction in heart failure of various etiologies.
- Cardiac MRI: accurate monitoring of RV mass and function for early detection of pulmonary hypertension, impending right heart failure.
- Radionuclide angiography.

C. TREATMENT OF ESTABLISHED HEART FAILURE OR SEVERE PULMONARY HYPERTENSION:

- Patients in heart failure require more frequent transfusions (two-week intervals) to maintain a pre transfusion hemoglobin of ~12.0 gm/dl.
- Diuretic therapy may be required during transfusions, accurate weight measurements at regular intervals and after-load reduction cardiac medication may be indicated.
- Frequent evaluation of serum electrolytes, calcium, and magnesium while on diuretic therapy is required.
- Coordinated patient care with cardiologist is required.
- Consideration of heart transplantation before severe refractory congestive heart failure due to cardiomyopathy.

VII. BONE MARROW TRANSPLANTATION (BMT)

Bone marrow transplantation is the only cure for thalassemia at this time. This therapy should be considered in all patients who have an acceptable donor. Patients are classified on the basis of their risk factors, which have been found to influence post transplant outcome. These include: inadequate chelation, presence of liver fibrosis and hepatomegaly.

- Patients should be referred to the nearest transplant center with experience with marrow transplantation of genetic disease.
- The liver, lungs, heart and maxilla are particular targets of complications of thalassemia and chronic transfusion. The following studies must be done prior to transplantation:
 - Staging of liver fibrosis and inflammatory lesions by liver biopsy, as per Knodell numerical scoring system (Knodell RG et al Hepatology1;431,1981).
 - Pulmonary function and cardiac studies.
 - Dental evaluation and restoration.
- Early referral to a transplant center is recommended, as BMT has a better outcome in younger patients.

A. IRON OVERLOAD AFTER A BMT:

After a successful BMT, continuous treatment of the preexisting iron overload is indicated:

- Perform a phlebotomy of 5 cc / kg / month until liver iron is less than 7.5 mg /g/ dry wt, can be done in conjunction with desferrioxamine therapy.
- If pre transplantation liver biopsy was done more than two years prior to institution of phlebotomy, consider repeating liver biopsy to confirm elevated liver iron status.
- Liver biopsy every 12 to 24 months to monitor hemosiderosis.
- Perform phlebotomies if hepatic iron at pre transplantation > 7 mg / g / dry wt, or Ferritin is greater than 2000 ng / ml.

VIII. OTHER SYSTEMS

A. DENTAL EVALUATION:

The teeth and maxillary occlusion can be significantly affected in patients with thalassemia. Proper transfusion therapy will prevent many of the changes. However, close dental and orthodontic monitoring is crucial. Furthermore, splenectomy can complicate dental care due to increased infection risk.

- Annual dental examination.

B. NUTRITION:

Nutritional deficiencies are common in thalassemia secondary to the use of desferrioxamine, the hemolytic anemia, and iron overload that accompanies this disease.

- Annual evaluation by registered dietitian of low iron diet and adequate dietary calcium, vitamin D, trace minerals (copper, zinc, and selenium) and antioxidant vitamins (E and C).
- Recommendation for diets and dietary supplementation as indicated by diet history and complications of disease.
- Counseling for patients with diabetes mellitus by a registered dietitian and endocrinologist.
- Counseling for patients with special dietary needs, such as during pregnancy.

C. VACCINATIONS:

As some patients will require splenectomy and all are exposed to infection from blood products, optimal immunization is critical for patients with thalassemia.

- Vaccination records should be checked annually.
- Immunization for hepatitis A and B.
- Annual Influenza vaccination.
- Annual PPD.
- 7-valent conjugate pneumococcal vaccine beginning at age 2 months as recommended, booster with 23-valent vaccine at age 5 to 10, check the pneumococcal titers following immunization. Severe local reactions can indicate high titers and can occur if titers are elevated.
- Prior to splenectomy, all vaccines should be up to date, in particular Hemophilus Influenza and Pneumococcal vaccines.

IX. THALASSEMIA INTERMEDIA

Thalassemia intermedia is a serious thalassemia syndrome which frequently does not receive the attention it deserves. Unlike thalassemia major where the level of anemia makes transfusion

mandatory, thalassemia intermedia patients may not have hemoglobin levels low enough to warrant mandatory blood transfusion and regular care. However, progression of both the anemia and ineffective erythropoiesis eventually result in serious complications. Many of the complications noted for thalassemia major occur in thalassemia intermedia. These result from ineffective erythropoiesis, anemia, dietary iron absorption and occasional transfusion. Patients experience bony changes, endocrinopathies, osteoporosis cardiac disease and pulmonary hypertension. The extent of these complications affects the decision of treatment intervention. Treatment modalities involve transfusions, splenectomy and medications which increase hemoglobin F synthesis. Standards of care are lacking for this important group of patients who suffer immeasurably due to an unpredictable degree of anemia and course.

A. Non-transfused Thalassemia Intermedia:

General Recommendations

- Patients should be followed at a thalassemia center every 3-6 months with attention to overall clinical well-being, anthropometrics as described for thalassemia major, change in exercise tolerance, complete blood count, reticulocyte count, and ferritin levels.
- A baseline red blood cell phenotype should be obtained.
- Attention to changes in facial bone structure. Obtain biannual skull x rays in growing children and facial photographs: anterior/posterior and lateral.
- Attention to growth velocity, especially in young children and in adolescents.
- Annual dental and orthodontia evaluation.
- Benefits and complications of splenectomy need to be discussed with the family and patient, particularly in cases of massive splenomegaly or hypersplenism.
- Recommend a low iron diet, and drinking tea with meals to decrease absorption of iron.
- Patients should receive immunizations as outlined for thalassemia major patients.
- The general recommendations for endocrine, growth, and iron status monitoring outlined for thalassemia major should be applied to patients with thalassemia intermedia. After the initial evaluations, the frequency of monitoring can be modified based on the degree of iron loading or growth failure.

Assessment of Iron Overload

- Ferritin and iron saturation levels should be monitored annually.
- If the ferritin is persistently greater than 1000 ng/ml or the iron saturation is greater than 60% obtain assessment of liver iron by ferritometer or liver biopsy.
- If ferritin is greater than 1500 ng/ml or if liver iron is greater than 6-mg/ gram dry weight begin chelation therapy.
- Use above guidelines for the administration of desferrioxamine.

Considerations in Starting Regular Transfusion Therapy

The decision to start regular transfusions depends on clinical and laboratory assessment: worsening anemia, inability to tolerate anemia, massive splenomegaly (if splenectomy is not entertained), worsening bone disease, increasing nucleated red blood cells and dropping hemoglobin. Skeletal malformation can be severe in thalassemia intermedia and should be considered in the decision to start transfusion. The decision to start chronic transfusion is not necessarily a permanent commitment to life long transfusion. These decisions are difficult and best made at a thalassemia center.

X. PSYCHOSOCIAL SUPPORT

Thalassemia imposes a significant intrusion in the lives of the patients and their families. The effects are many, sweeping from financial hardships and absence from school and work, to significant issues with self-image and self esteem. All of these issues have a tremendous impact of the effectiveness of therapy and on the quality of life of the patients. These challenges are further complicated by normal stages of development incurred from infancy to adulthood and by vast cultural differences. This latter point cannot be emphasized enough. Because of the ethnic predilection of thalassemia, the patients come from diverse cultural backgrounds, which are usually different from those of their healthcare provider. Thus, all professionals who provide care and support to these patients must be aware of the cultural, social, developmental, and behavioral issues that affect this diverse population. Medical and psychosocial professionals must also be intimately involved with each other in order to provide optimal care to their

patients. Referral to outside providers who have no knowledge or understating of the medical problems is generally ineffective. Behavioral problems have great bearing on compliance with therapy and thus with medical outcome as well as with quality of life for patients with chronic disease.

A. CHILD LIFE SERVICES:

Culturally sensitive child life services are an integral part of a patient's comprehensive care. Child life services assure that care is family centered and developmentally appropriate for the patient. It is imperative that patients with Thalassemia understand their disease and treatment in order to comply with their rigorous medical regime. Child life programs in health care settings minimize psychological trauma and promote optimal development of children and their families.

- Through observation and discussion, assess the response of the patient and family to health care experiences and develop a plan to meet their needs and assist with coping.
- Provide opportunities for gaining a sense of mastery, for play, for learning, for self-expression, for family involvement and for peer interaction. This can be achieved in many ways including medical play and art therapy.
- Provide a positive growth experience for patients. Minimize stress and anxiety for the patient, parents, and siblings.
- Prepare children and families for health care experiences. Example: conduct a medical preparation prior to a patient's liver biopsy and splenectomy. This increases overall understanding of the procedure and reduces anxiety.
- Provide essential life experiences such as play, school, peer-interaction, community events and activities. These experiences commonly take place in a playroom or schoolroom.
- Create opportunities that strengthen self-esteem and independence.
- Child life specialist communicates and collaborates with other members of the health care team.

B. PSYCHOLOGICAL SERVICES:

Cultural sensitive psychological services make up a critical part of all comprehensive care plans for patients with chronic illness. In particular, those with rare chronic diseases that have high morbidity and require time intensive therapy and medical intervention such a thalassemia. Several sessions of therapy with a psychologist, is recommended for all patients starting at adolescent (or earlier if indicated) to help cope with issues related to the morbidity of thalassemia and fear of dying.

- Evaluation of general functioning and adaptation to chronic illness and to local culture.
- Evaluation of ability to comply with and cope with medical regimen.
- Assistance and intervention with issues of compliance and coping styles should be considered for every patient.
- Organization and direction of therapeutic groups for adolescents and adults.
- Evaluation and referral to psychiatrist for administration of psychotropic medication.

C. SOCIAL SERVICES:

Social services that meet the needs of the patients in a culturally sensitive way are critical for patients with chronic disease that requires an inordinate amount of resources.

- Evaluation of functioning in the community and school.
- Provision for adequate social and medical services.
- Services for assessment of medical need and financial assistance.

D. GENETIC COUNSELING:

Culturally sensitive genetic counseling is required for parents and patients affected by this disease. Reproduction is a major issue with all families who carry genetically transmitted diseases.

- Education and counseling.
- Annual teaching and evaluation of understanding of disease.
- HLA typing of full siblings, available parents.
- Reproductive teaching for adolescents.
- Referral to gynecologist or fertility specialist if indicated.
- Counseling during pregnancy.