Treatment of beta thalassemia

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INTRODUCTION — In normal subjects, globin chain synthesis for hemoglobin is very tightly controlled, such that the ratio of alpha to non-alpha chains is 1:1. Thalassemia refers to a spectrum of diseases characterized by reduced or absent production of one of the globin chains of hemoglobin. Specifically, beta thalassemia is due to impaired production of beta globin chains, which leads to a relative excess of alpha globin chains. Excess alpha globin chains are unstable, incapable of forming soluble tetramers on their own, and precipitate within the cell, leading to a variety of clinical manifestations. The degree of alpha globin chain excess determines the severity of subsequent clinical manifestations, which are profound in patients homozygous for impaired beta globin synthesis and much less pronounced in heterozygotes, who generally have minimal or mild anemia and no symptoms. (See "Pathophysiology of beta thalassemia".)

The management of beta thalassemia will be reviewed here [1,2]. The clinical manifestations of this disorder are discussed separately. (See "Clinical manifestations and diagnosis of the thalassemias".)

DEFINITIONS — Certain clinical terms are used to describe the phenotypic expression of beta thalassemia (see "Pathophysiology of beta thalassemia"):

- **Beta (0) thalassemia** – Beta (0) thalassemia refers to mutations of the beta globin locus that result in the **absence** of production of beta globin. Patients homozygous or doubly heterozygous for beta (0) thalassemic genes cannot make normal beta chains and are therefore unable to make any hemoglobin A.
- **Beta (+) thalassemia** – Beta (+) thalassemia refers to mutations that result in **decreased** production of beta globin. Patients homozygous for beta (+) thalassemic genes are able to make some hemoglobin A, and are generally less severely affected than those homozygous for beta (0) genes.
- **Beta thalassemia major** – Beta thalassemia major is the term applied to patients who have either no effective production (as in homozygous beta (0) thalassemia) or severely limited production of beta globin. These are the patients originally described by Cooley (Cooley's anemia). Starting during the first year of life, they have profound and life-long transfusion-dependent anemia.
- **Beta thalassemia minor** – Beta thalassemia minor (beta thalassemia trait) is the term applied to heterozygotes who have inherited a single gene leading to reduced beta globin production. Such patients are asymptomatic, may be only mildly anemic, and are usually discovered when a blood count has been obtained for other reasons.
- **Beta thalassemia intermedia** – Beta thalassemia intermedia is the term applied to patients with disease of intermediate severity, such as those who are compound heterozygotes of two thalassemic variants (table 1). These patients have a later clinical onset and a milder degree of anemia, which may or may not require transfusional support.

MANAGEMENT — Management of beta thalassemia varies with the type of disease, which will be described below for each of the three beta thalassemia variants listed above.

Beta thalassemia minor — Subjects with beta thalassemia minor (beta thalassemia trait) are not symptomatic from this condition, may have only mild degrees of anemia, and require no specific therapy. Transfusions are

occasionally required in pregnant women who may develop a more severe "physiologic" anemia of pregnancy. It is important that this condition be diagnosed properly, as it is often confused with iron deficiency anemia and does not respond to treatment with iron. (See "Clinical manifestations and diagnosis of the thalassemias", section on 'Beta thalassemia minor'.)

However, patients with thalassemia minor share the same general risk as normal individuals for development of iron deficiency anemia from other causes. They should not be denied iron when true iron deficiency and beta thalassemia trait coexist. (See "Causes and diagnosis of iron deficiency anemia in the adult" and "Treatment of the adult with iron deficiency anemia".)

Beta thalassemia intermedia — Patients with thalassemia intermedia are prone to develop many of the complications seen in patients with beta thalassemia major (eg, leg ulcers, osteoporosis, extramedullary hematopoiesis, hypogonadism, gallstones, aplastic crisis, secondary folate deficiency). The effect of various treatments (eg, transfusion, HU, splenectomy) on the risk of these complications is unclear [3-5].

Anemia and transfusions — Patients with beta thalassemia intermedia must be monitored closely for progression of their anemia, and/or the development of worsening evidence of the complications of hemolysis or extramedullary erythropoiesis [6]. In the majority of these patients, chronic transfusion therapy will ultimately have to be implemented, occasionally as late as the third or fourth decade of life. Symptoms usually develop when the hemoglobin level falls below 7 g/dL, and transfusion may be required during periods of rapid growth, infection-associated aplastic crises, surgery, and pregnancy [7,8]. However, in some settings, severe degrees of anemia can be well tolerated, such as in those with hemoglobin E/beta thalassemia [9]. Accordingly, the patient's activity limitations, growth, development, and the early appearance of skeletal changes or other disease-related complications are the factors that need to be taken into consideration when considering a transfusion program [3]. (See 'Chronic hypertransfusion therapy' below.)

Earlier transfusion may be reasonable in order to maintain growth and increase well being in the child with thalassemia. In addition, the risk of developing alloimmunization may be lessened by earlier transfusion.

- In one study in 1200 patients with thalassemia, the prevalence of alloimmunization to red cell transfusions was 21 versus 48 percent in thalassemic subjects who received their first transfusion before or after the age of three years, respectively [10].
- In a second report in 297 patients, most of whom had beta thalassemia major, the rate of alloimmunization was 11 percent for those first transfused before the age of one year, and was 18 to 31 percent in those first transfused after that age [11].

Other options for decreasing the transfusion requirements in patients with thalassemia intermedia include the following:

- Folic acid supplementation – Folate requirements are increased in those with increased erythropoiesis. It is therefore reasonable to treat all thalassemia intermedia patients with oral folic acid, in a dose of 1 to 2 mg/day. (See 'Supportive measures' below.)
- Splenectomy – Institution of transfusion therapy can be delayed by splenectomy if anemia or other symptoms worsen significantly (picture 1). (See 'Splenectomy' below.)
- Hydroxyurea – The use of hydroxyurea (HU), with or without supplemental erythropoietin, is discussed below. (See 'Hydroxyurea' below.)

When to initiate transfusion therapy — One of the most difficult decisions in the management of adults with thalassemia intermedia is when to initiate chronic transfusion therapy. These patients accumulate complications as they move into the fourth to seventh decade of life, including progressive iron overload with end organ dysfunction, development of congestive heart failure, renal insufficiency, pulmonary hypertension due to anemia, progressive splenomegaly, and growth of masses of extramedullary hematopoiesis, which can impinge on

nerves, vessels, and the spinal column. While no level 1 evidence to guide this decision is available, a trial of hypertransfusion (eg, regular infusion of red cells [two units of packed RBCs every two to four weeks is a good starting point]) should be initiated if and when:

- The patient shows signs of cardiopulmonary compromise, or significant deterioration of functional status that responds to acute transfusion support.
- Development of signs or symptoms of progressive marrow expansion (eg, masses of extramedullary hematopoiesis, pathologic fractures, progressive organomegaly).

Iron chelation should commence upon initiation of hypertransfusion. These patients are already iron overloaded from the expanded erythron and ineffective erythropoiesis. (See 'Iron overload' below.) As with patients with beta thalassemia major and sickle cell anemia who require long-term transfusion support, units for transfusion should be chosen with great care in association with a knowledgeable blood bank to minimize the risk of allo-immunization. (See 'Initiation of treatment and avoidance of complications' below.)

Splenectomy — Splenectomy in patients with thalassemia intermedia is generally indicated for growth retardation, poor health, leukopenia, thrombocytopenia, increased transfusion need, or symptomatic splenomegaly [12]. However, a high incidence of thromboembolic complications, both arterial and venous, has been noted following splenectomy [13-15], leading to the suggestion that splenectomy be avoided in this population if at all possible [3], even if this choice entails a greater need for red cell transfusion and the subsequent need for iron chelation because of transfusional iron overload and its consequences [16].

In one study, splenectomized patients with thalassemia intermedia who developed a documented thromboembolic event were more likely to have a nucleated red cell count ≥300 cells/microL, a platelet count ≥500,000/microL, to be transfusion naïve, or to have evidence for pulmonary hypertension [17]. Subjects with any of the first three of these four characteristics also had a shorter time to thrombosis following splenectomy.

While this and other studies have suggested the use of antiplatelet/anticoagulant therapy in high-risk patients with thalassemia intermedia (eg, major surgery, pregnancy, post-splenectomy), controlled studies indicating the safety and utility of this approach are not available [8,13,18-20].

Iron overload — Patients with beta thalassemia intermedia eventually develop iron overload even without the use of blood transfusions, because of the increased iron absorption associated with high rates of erythropoiesis and red cell destruction. Thus, iron stores in these patients should be monitored on a regular basis. Magnetic resonance imaging (MRI) appears to be superior to measurement of serum ferritin for estimating total body iron burden in these patients, especially those who are being regularly transfused [21-24]. As an example, when compared to subjects with beta thalassemia major, serum ferritin levels in those with thalassemia intermedia tend to underestimate the degree of iron loading as reflected in liver iron concentrations [25,26].

Iron chelation therapy is indicated if serum ferritin concentrations are excessive and/or if imaging and other studies suggest the presence of iron loading in critical organs such as the liver and heart [3,27-29]. The general subject of transfusional iron overload and the indications for initiation of iron chelation in beta thalassemia intermedia are discussed in depth separately. (See "Iron overload syndromes other than hereditary hemochromatosis", section on 'Transfusional iron overload' and "Chelation therapy for thalassemia and other iron overload states", section on 'Iron chelation in transfusion-independent thalassemia'.)

Because the tannins in tea chelate iron in the intestinal tract and prevent or reduce the absorption of dietary iron, regular consumption of tea is encouraged, although evidence for its efficacy is incomplete [30]. (See "Approach to the patient with suspected iron overload", section on 'Diagnosis of iron overload'.)

Cardiopulmonary complications — Patients with beta thalassemia intermedia may suffer from the complications of chronic hypoxia, such as high cardiac output, increased pulmonary vascular resistance, pulmonary hypertension, and resulting heart failure [31,32]. Although physical examination can be used to screen for the presence of right-sided cardiac changes, it has been suggested that serial screening via Doppler

echocardiography (eg, Doppler tricuspid gradient measurement) may be the best noninvasive technique for establishing the presence of these complications [31]. (See "Clinical features and diagnosis of pulmonary hypertension in adults" and 'Pulmonary hypertension' below.)

Initiation of transfusion-chelation therapy is warranted if cardiopulmonary complications are seen in patients with thalassemia intermedia [33], although it would appear preferable to initiate transfusion therapy in these patients in order to prevent, rather than palliate, such complications [6]. (See 'Chronic hypertransfusion therapy' below and "Iron overload syndromes other than hereditary hemochromatosis", section on 'Transfusional iron overload'.)

Leg ulcers — Chronic leg ulcers are present in approximately 8 percent of patients with thalassemia intermedia. Risk factors for this complication are unclear, but may include older age, chronic anemia, high levels of HbF with decreased oxygen delivery to the tissues, right heart failure, iron overload, and a hypercoagulable state following splenectomy [4,34]. Similarly, there is only anecdotal evidence for the effective treatment of this complication, which has included such modalities as blood transfusion, hydroxyurea, iron chelation, hyperbaric oxygen, anticoagulation, plastic surgery, and the use of granulocyte macrophage colony-stimulating factor [4,34-37].

Other complications — Because of enlargement of the facial bones secondary to extramedullary hematopoiesis, surgical correction of the maxilla may be needed, as are folic acid supplementation and close monitoring for biliary tract disease secondary to the presence of bilirubin-rich gallstones.

Beta thalassemia major

Overview — Prior to the advent of hypertransfusion regimens in the 1960s, beta thalassemia major was a disease fatal in infancy. Observational studies have shown that hypertransfusion regimens transformed this disorder into a more chronic disease, with subjects usually dying in their second decade of life from the complications of transfusional iron overload. Iron chelation therapy, begun in the 1970s, transformed this into a chronic disease permitting prolonged survival. Hematopoietic cell transplantation, begun in the 1980s, is a curative regimen, although not all patients are candidates for this procedure. (See "Efficacy of hematopoietic cell transplantation in beta thalassemia major".)

Accordingly, the mainstays of therapy for beta thalassemia major are chronic hypertransfusion combined with iron chelation, and supportive measures directed at the complications of the expanded erythron and iron overload [38,39]. Emerging therapies include the wider use of allogeneic bone marrow transplantation, the only curative modality, pharmacologic manipulation of fetal hemoglobin levels, and, eventually, it is to be hoped, gene therapy [40]. Optimal care of these patients requires coordination among these modes of therapy and ongoing decision-making about their applicability or inapplicability to each individual patient or family.

Chronic hypertransfusion therapy — The widespread acceptance of chronic hypertransfusion as the therapy of choice for severe beta thalassemia has greatly altered the typical clinical course for patients in areas of the world with sufficient resources to support hypertransfusion programs [41-43]. Transfusion was once used only as a palliative or emergency measure in these patients because of limited availability of blood, fears about the complications of transfusion, and/or concerns about the long-term development of iron overload. While intermittent blood transfusion may have sustained patients through acute crises, it provided little in the way of beneficial effects on the progression of the syndrome. In particular, this approach did nothing to check the ravages that massive ineffective erythropoiesis and erythroid hyperplasia inflicted upon the growth, development, and systemic well being of the child with beta thalassemia major.

For these reasons, chronic hypertransfusion regimens were introduced in the 1960s [38]. These regimens shared in common the strategy that transfused red cells were to be given often enough and in sufficient quantity to maintain a "steady state" hemoglobin level of 9 to 10 g/dL. During the initial phases, this required an increase of about 125 percent in the amount of administered blood. There was considerable fear that this increase would accelerate the rate of iron overload and shorten patient survival. However, as discussed below, this fear was not realized, possibly because hypertransfusion-induced reduction in erythropoiesis also reduces the increased absorption of iron from

the gastrointestinal tract. Moreover, suppression of erythropoiesis probably reduces the expanded blood volume otherwise required to supply the hyperplastic marrow. This combination of effects may ultimately lead to a stabilization of long-term chronic red cell requirements [22,38].

Benefits — The clinical benefits of hypertransfusion begun during the first decade of life are dramatic, with reductions in hepatosplenomegaly, partial correction of abnormal skeletal development, and at least short-term improvements in cardiac dilatation and systolic function. In most industrialized countries, hypertransfusion regimens have become the norm. As a result, the most dramatic clinical features of severe thalassemia are rarely encountered in these countries [38,41,42]. It is now well established that chronic hypertransfusion improves oxygen-carrying capacity, cardiac status, and systemic parameters of growth, development, and overall well being. Attendance at school is improved, intercurrent infections appear to be reduced, and overall health appears to be greatly improved during the first 10 to 15 years of therapy. (See 'Overview' above and "Clinical manifestations and diagnosis of the thalassemias".)

Initiation of treatment and avoidance of complications — Transfusion therapy should be started early in those children clearly exhibiting the stigmata of beta thalassemia major. As noted above, the time to institute therapy in patients with thalassemia of intermediate severity is much less clear and requires close clinical monitoring. (See 'When to initiate transfusion therapy' above.)

Before the first transfusion is given, it is important that extended phenotyping of the patient's red cells for Rh Subgroups and minor red cell antigens be performed [21,38,44]. As an example, in two series of children and adults with thalassemia, the vast majority of the alloantibodies formed were directed against Kell and Rh subgroups (eg, C and E) [11,45]. Given the life-long requirement for frequent transfusions, all possible steps to eliminate alloimmunization must be taken from the onset. This may include attempts at matching donors of the same ethnic origin, as well as the potentially beneficial effects of leukodepletion [44,46,47]. (See "Red blood cell transfusion in sickle cell disease", section on 'Transfusion techniques' and "Red blood cell transfusion in sickle cell disease", section on 'Hemolysis and alloimmunization'.)

Debate currently exists as to whether other steps to avoid related complications (eg, febrile reactions, delayed transfusion reactions, transfusion-related graft versus host disease) should be undertaken routinely in this patient group. Thus, most centers use frozen red cells, leukocyte-poor red cells and/or washed red cells; widespread use of irradiated red cells is not currently the norm [11]. These patients are at risk for all of the usual blood-borne infections (eg, hepatitis C, HIV), which may have been acquired from areas that are still not providing uniform infectious screening of red cell transfusions, and need to be closely monitored for symptoms or laboratory abnormalities indicative of active infection, as well as the longer-term complications of fibrosis, cirrhosis, and hepatocellular carcinoma.

Complications — A report from the CDC Thalassemia Blood Safety Network has summarized transfusion complications in the 407 thalassemia patients enrolled in this program between 2004 and 2011 in seven participating centers in the United States. Findings included the following [11]:

- As expected, all of the 327 chronically transfused patients had iron overload (median ferritin levels 1376 mcg/L) and 78 percent of the entire group of 407 patients had received chelation therapy.
- At study entry, 86 patients' (24 percent) intake forms revealed previous exposure to possible transfusion-associated infectious diseases, including hepatitis C (61), hepatitis B (20), hepatitis A (three), parvovirus (nine), HIV (four), and one case each for S. aureus, malaria, and Babesia.
- A history of transfusion reactions was reported in 48 percent of the transfused patients. Of those with transfusion reactions, 52 percent were allergic, 16 percent were febrile, and 27 percent had reactions of varied types. There were 17 hemolytic transfusion reactions, of which nine were immune in nature.
- Nineteen percent of the transfused patients had alloantibodies; 47 percent of alloimmunized patients had multiple alloantibodies. Anti-E, anti-K, or anti-C were identified in the majority (70 percent). Alloimmunization

was significantly more common in those who were splenectomized (31 versus 11 percent in the nonsplenectomized group). In the chronically transfused patient group, the age at which patients began transfusions was significantly associated with alloimmunization and was 11 percent in those who began transfusion before one year of age and 18 to 28 percent in those transfused after one year of age.

- Autoantibodies occurred in 6.5 percent of patients, 84 percent of which were also alloimmunized. In a multivariate model that included age, splenectomy status, presence of alloantibodies, and years of transfusion exposure, only the presence of an alloantibody was a significant independent predictor of autoimmunization.
- Of importance, local blood banking practices varied considerably among the seven participating centers. For those transfused in the year before study entry, 31 percent received blood matched only for ABO/D, 38 percent were also matched for C, E, and Kell, and 10 percent received extended phenotypically matched red cells. Red cells were leukoreduced in 94 percent, washed in 35 percent, and irradiated in 33 percent.

Hepatocellular carcinoma — Both hepatic hemosiderosis and transfusion-transmitted hepatitis (ie, HBV and HCV) are risk factors for the development of hepatocellular carcinoma (HCC) in individuals with beta thalassemia intermedia and major. According to an Italian Registry, between 2002 and the end of 2012, 60 new cases of HCC were reported among the 5855 patients followed by the participating centers, for a cumulative incidence of 1.02 percent. The following observations were made [48]:

- Of the 60 reported cases, 36 showed evidence of past HBV infection, 54 had antibodies against HCV, and four had no evidence of exposure to either virus. Eighty-two percent of the patients were either asymptomatic at the time of diagnosis of HCC or complained of non-specific symptoms.
- At the time of diagnosis of HCC, the mean liver iron concentration was 8 mg/g dry weight, the median level of serum ferritin was 1041 mcg/L, and the median peak serum ferritin was 2460 mcg/L. The alpha-fetoprotein level was within the normal range in 20 of the 45 patients in whom it was available.
- The average survival time from HCC detection to death was 11.5 months. Because of the poor survival following detection of this complication, as well as the fact that the vast majority (82 percent) were asymptomatic at the time of diagnosis, it was recommended that ultrasonography be performed every six months in this population, especially in those at high risk for HCC (eg, iron overload, HCV, HBV, advanced fibrosis or cirrhosis), in the hope that they might be candidates for treatment (eg, surgical resection, loco-regional therapy, liver transplantation) [49]. (See "Overview of treatment approaches for hepatocellular carcinoma".)

Hypertransfusion regimen — Depending on the size of the patient, the usual transfusion regimen involves infusion of one to three units of packed red cells every three to five weeks [41-43]. More frequent transfusions may be required initially. Some centers favor an initial "super transfusion" to hemoglobin levels of 12 to 14 g/dL, in the hopes that, over the long term, the same chronic blood requirement would maintain a higher hemoglobin concentration and, presumably, more normal physiologic function [22]. The efficacy of these regimens remains unproven. Occasional reports of bizarre reactions occurring within the first 24 to 48 hours after transfusion have led to the recommendation that no more than 15 mL of red cells per kg of body weight be administered during any 24-hour period, except in cases of profound emergency.

Cardiac monitoring — Frequent monitoring of cardiac function in transfusion-dependent patients may indicate those at risk of developing symptomatic cardiac disease, who might then be candidates for more intensive and sustained transfusional regimens, iron chelation therapy, and the use of cardioactive drugs [50]. In one study, 81 patients with thalassemia major and no history of cardiac disease underwent quantitative annual monitoring of left ventricular ejection fraction (LVEF) by radionuclide ventriculography for a median of six years. The following observations were made [51]:

- An absolute LVEF <45 percent or a decrease of >10 percentage units was significantly associated with subsequent development of symptomatic cardiac disease and death, with a median interval between the first

abnormal LVEF findings and development of symptomatic cardiac disease of 3.5 years.

- Heart failure and/or arrhythmia, as well as death, were less common in those in whom subcutaneous iron chelation was started before 10 years of age as well as in those who had a serum ferritin >2500 microg/L for less than one-third of follow-up time.

- Intensified sustained iron chelation therapy was recommended in 34 patients in whom LVEF was <45 percent or decreased by >10 percentage units. All 27 patients complying with intensification survived, while all seven who did not comply died. (See "Iron overload syndromes other than hereditary hemochromatosis", section on 'Transfusional iron overload'.)

Development of acute decompensated heart failure — Development of acute decompensated heart failure is the major cause of death in beta thalassemia major, and constitutes a **medical emergency**, requiring urgent consultation with a medical center having expertise in its management [52].

A 2013 consensus statement from the American Heart Association, endorsed by the Thalassaemia International Federation, European Society of Cardiology Working Group on Cardiovascular Magnetic Resonance, and the Society for Cardiovascular Magnetic Resonance, suggests that the first principle of management should include urgent commencement of a continuous, uninterrupted infusion of high-dose intravenous deferoxamine (50 mg/kg per day), augmented by oral deferiprone (total dose 75 mg/kg per day, given in three divided doses) [52].

Supportive therapy should include continuous electrocardiographic and hemodynamic monitoring, normalization of electrolyte abnormalities, maintenance of meticulous glucose control, correction of other metabolic parameters (eg, calcium, magnesium, thyroid, hepatic, and renal function), and a search for other precipitating factors (eg, infection). (See "Treatment of acute decompensated heart failure: Components of therapy".)

Supportive treatment of acute heart failure for those with beta thalassemia differs from that routinely provided in the following ways [52]:

- Supportive hemodynamic therapy should be geared to maintain cerebral and renal perfusion, avoiding aggressive inotropic therapy, which can be detrimental. Blood pressure is typically low in these patients and should not attract specific therapy if cerebral and renal perfusion is maintained.

- Only minimum diuretic treatment should be used because of the importance of maintaining preload.

Splenectomy — An indication for splenectomy in patients with beta-thalassemia major and intermedia is an increase of 50 percent or more in the red cell transfusion requirement over a one-year period [1]. Splenectomy is usually associated with a reduction in red cell transfusion requirement, although the benefit is often transient.

Post-splenectomy thrombocytosis is common, and is a risk factor for thromboembolic events [18,53,54]. However, thromboembolic complications in splenectomized patients with beta thalassemia major are not as frequently noted when compared to patients with thalassemia intermedia who have undergone splenectomy [19,55]. (See 'Splenectomy' above.)

Because such spleens may be quite large, the laparoscopic technique may not always be technically possible, and may be associated with a higher incidence of portal vein thrombosis [56,57]. The decision to pursue splenectomy is therefore a difficult one, and should be made on a case-by-case basis, as there is a fine balance between benefits and risks in this condition.

Iron chelation therapy — Iron overload is inevitable in patients requiring life-long transfusion support. Each unit of transfused red cells introduces 200 to 250 mg of elemental iron into the body. Since iron cannot be actively excreted, and is utilized poorly in patients with ineffective erythropoiesis associated with beta thalassemia major, the excess iron is deposited in other viscera, usually the liver, heart, and endocrine organs. When iron stores overwhelm the ability of reticuloendothelial cells to sequester them, parenchymal iron overload develops, leading to end-organ dysfunction (especially heart, liver, and endocrine organs) and death [41-43].

The typical thalassemic child receiving a hypertransfusion regimen has an intake of 8 to 16 mg of elemental iron per day, in contrast to 1 to 2 mg/day typical of normal subjects [43,58-60]. Even though hematopoiesis is partially suppressed by hypertransfusion, accelerated oral iron absorption also contributes to the total iron overload. Aggressive attempts to remove iron from the body pharmacologically are necessary. Clearly, phlebotomy, the most efficacious way to remove iron in other patient groups (eg, hereditary hemochromatosis), is not an option in subjects requiring transfusion.

Iron chelation therapy is initiated before the age of six years, often as early as two to four years of age, after approximately 20 to 25 units of red cells have been transfused, at a time when the serum ferritin level is >1000 ng/mL (mcg/L) and the child's liver iron concentration is >3 mg of iron per gram of dry weight as measured either by liver biopsy of noninvasive MRI imaging [1]. (See "Approach to the patient with suspected iron overload", section on 'Diagnosis of iron overload' and "Chelation therapy for thalassemia and other iron overload states".)

Once initiated, an iron chelation program must be rigorously followed and frequently monitored using MRI techniques [61-63], in order to be medically effective, to prevent myocardial iron overload and subsequent myocardial dysfunction, stabilize or improve endocrine dysfunction, and to prepare the patient for possible hematopoietic cell transplantation at a later date. (See "Clinical manifestations and diagnosis of the thalassemias", section on 'Magnetic resonance imaging' and "Efficacy of hematopoietic cell transplantation in beta thalassemia major".)

This important subject is discussed in depth separately. (See "Iron overload syndromes other than hereditary hemochromatosis", section on 'Transfusional iron overload' and "Iron overload syndromes other than hereditary hemochromatosis", section on 'Chelation therapy' and "Chelation therapy for thalassemia and other iron overload states".)

Osteoporosis — Osteopenia with cortical thinning, and severe osteoporosis with fractures remain serious complications of beta thalassemia major, even in well-transfused and iron-chelated patients. The mechanisms underlying this complication are unclear. (See "Clinical manifestations and diagnosis of the thalassemias", section on 'Skeletal changes'.)

Treatment of osteoporosis, an important cause of morbidity in adult patients with thalassemia major, requires a concerted, multidisciplinary approach, and includes the following components, although evidence for their effectiveness is incomplete [64,65]:

- Bone mineral density studies, starting in adolescence
- Encouragement of moderate to high impact physical activity
- Avoidance of smoking
- Adequate calcium, zinc, and vitamin D intake
- Early diagnosis and treatment of diabetes mellitus
- Prevention and/or correction of hypogonadism [66]
- Adequate iron chelation
- Blood transfusions to inhibit excessive bone marrow expansion
- Potential use of agents that inhibit osteoclast activity (eg, calcitonin, bisphosphonates) [66-69]
- Potential use of agents/interventions that increase bone formation [70]

Supportive measures — Continuity of care is essential for improving the morbidity and mortality of children with severe thalassemia [41-43,58-60]. In addition to close monitoring of transfusion and iron chelation therapy, patients need to be under surveillance for a variety of associated symptoms of anemia and iron overload. These include close monitoring during the ages surrounding puberty for development of primary and secondary sexual characteristics, with appropriate endocrine consultation for intervention if growth, development, and puberty are delayed. (See "Normal puberty".) In addition, patients with severe thalassemia are at risk for aplastic crisis from infection with parvovirus B19, during which time transfusion requirements may increase dramatically.

Repletion with folic acid because of an increased need secondary to increased erythropoiesis (1 to 2 mg/day by mouth) and a cautious use of ascorbic acid (for improving the effectiveness of iron chelation) and zinc supplementation (for its possible beneficial effect on osteoporosis) are indicated for reasons outlined above. Use of antioxidant compounds, such as vitamin E, remains controversial. Although a theoretical basis exists for their use, clinical efficacy has not been proven.

The cardinal manifestations of untreated beta thalassemia major (eg, bony fractures, development of masses of extramedullary hematopoiesis, abnormal facies, and dentition) are minimized when proper transfusion therapy is utilized. Nonetheless, patients should be monitored for the development of any suspicious signs or symptoms. Splenectomized patients require appropriate vaccination, and the use of prophylactic antibiotics. (See "Prevention of sepsis in the asplenic patient".)

Pulmonary hypertension — Patients with beta thalassemia major or intermedia may develop pulmonary arterial hypertension (PAH), a common sequel of the hemoglobinopathies associated with hemolytic anemia. (See "Pulmonary hypertension associated with sickle cell disease", section on 'Introduction'.)

Reports on the management of PAH in thalassemics (Group 1 PAH, formerly called idiopathic PAH) have included treatment with phosphodiesterase type 5 inhibitors (sildenafil) and the endothelin receptor antagonist bosentan, with anecdotal reports of success [71-75]. (See "Treatment of pulmonary hypertension in adults", section on 'Advanced therapy'.)

Hematopoietic cell transplantation — Hematopoietic cell transplantation (HCT) has, since the 1980s, become established as an important modality for patients with severe beta thalassemia. There is now extensive experience with HCT in these children, with well over 1000 patients having undergone this procedure. The use of HCT in severe beta thalassemia, including the relative value of medical treatment versus HCT is discussed in detail separately. (See "Efficacy of hematopoietic cell transplantation in beta thalassemia major" and "Specific issues related to hematopoietic cell transplantation in beta thalassemia".)

Pregnancy — With advances in hypertransfusion and iron chelation, some women with beta thalassemia major have had favorable pregnancy outcomes [76,77]. However, such pregnancies are generally recommended only in those with normal cardiac function and adequate hypertransfusion and iron chelation regimens [77,78].

A study from North America and the United Kingdom identified 129 pregnancies in 72 women among the 264 women, age 18 years or older, who were enrolled in the Thalassemia Clinical Research Network. Details concerning these pregnancies included the following [79]:

- Over 70 percent of the pregnancies resulted in live births, with 88 percent of live births occurring at term. Seventy-eight percent were conceived without the use of reproductive technologies.
- Pregnancy outcomes other than live births included miscarriage (12 percent) and elective termination (13 percent); reasons for the terminations were not collected in this study.
- Most pregnancies (59 percent) occurred while the mothers were on chronic transfusion programs, although only 39 percent were receiving iron chelation.
- The iron burden (eg, serum ferritin, liver iron content, cardiac T2*) in women who had conceived was not significantly different from age- and diagnosis-matched controls who had never become pregnant. There was also no difference in pregnancy outcomes associated with diagnosis, transfusion status, diabetes, or hepatitis C infection.
- Cardiac issues developed during pregnancy or delivery in four women and included atrial fibrillation during labor, peripartum left ventricular dysfunction, and left atrial enlargement. All resulted in live births and all women recovered.
- Four women developed diabetes mellitus or existing diabetes worsened during their pregnancy.

Genetic counseling for women with beta thalassemia of child-bearing age is strongly advised, since mothers with homozygous beta thalassemia will be transmitting a thalassemic gene to **all** of their offspring, and partnership with a male with beta thalassemia trait will lead to beta thalassemia major or intermedia in one-half of their offspring. (See "Community public health issues and the thalassemic syndromes: Lessons from other countries", section on 'Genetic counseling of couples'.)

MANIPULATION OF FETAL HEMOGLOBIN SWITCHING — The development of pharmacologic agents capable of promoting substantial levels of fetal hemoglobin synthesis (HbF) during adult life is a promising approach, even though clinical efficacy has not yet been demonstrated in patients with severe thalassemia [80,81]. Continuation of significant degrees of fetal hemoglobin synthesis might reduce clinical severity by providing additional hemoglobin for oxygen transport and reducing the burden of free alpha globin chains [82,83]. (See "Fetal hemoglobin (hemoglobin F) in health and disease".)

After many years of study in animal and tissue culture models, it was realized that certain cytotoxic drugs, commonly used in cancer chemotherapy, could elevate fetal hemoglobin synthesis in adults [21]. This effect appears to be due to their alteration of the genetics of primitive stem cells, some of which retain the potential to synthesize fetal hemoglobin. Under normal circumstances, very few of these clones enter the cell cycle for differentiation and maturation into erythroblasts and reticulocytes. Thus, fetal hemoglobin synthesis normally comprises only 0.5 to 1 percent of total adult hemoglobin synthesis. Furthermore, this small percentage is confined to a minor subpopulation of red cell clones called "F cells." Several cytotoxic drugs and other forms of severe bone marrow stress (eg, bone marrow transplantation [84], recovery from radiation or other bone marrow suppressants) increase the number of F cell clones, thus increasing fetal hemoglobin synthesis. (See "Fetal hemoglobin (hemoglobin F) in health and disease", section on 'Hemoglobin F containing cells' and "Fetal hemoglobin (hemoglobin F) in health and disease", section on 'Acquired increases in HbF'.)

Hydroxyurea — Hydroxyurea (HU), a cytotoxic drug commonly used in the treatment of myeloproliferative disorders, has been shown to increase fetal hemoglobin synthesis in patients with beta thalassemia, sickle cell disease, and some individuals with no hemoglobinopathy [85,86]. The effect of HU appears to be somewhat unpredictable in terms of the maximum HbF levels achieved in an individual patient, but the effect is dose-related and reversible within individual patients. Toxicity of HU is largely that of myelosuppression, which, in contrast to many similar agents, is rapidly reversible upon dose reduction or cessation of the drug treatment.

HU has achieved increasing clinical usage in sickle cell anemia, where it has been shown to reduce the frequency and severity of acute chest syndrome and painful crises. The use of HU has also been helpful in some patients with beta thalassemia intermedia [87-92], although its successful use in beta thalassemia major has been less frequently noted [85,86,90,91,93]. One small study obtained responses to HU in 8 of 16 patients with transfusion-dependent beta thalassemia with milder phenotype [94]. However, efforts to define inherent differences between responders and non-responders on the basis of preexisting gene expression patterns and clinical parameters have not yielded definitive results. (See "Hydroxyurea and other disease-modifying therapies in sickle cell disease", section on 'Reactivating fetal hemoglobin synthesis' and "Clinical variability in sickle cell anemia", section on 'Control of HbF expression'.)

Possible reasons for the discrepancy between the effectiveness of HU in sickle cell disease and beta thalassemia include the fact that patients with beta thalassemia major have a considerably higher quantitative requirement for fetal hemoglobin synthesis before clinical impact occurs. In addition, patients with severe beta thalassemia are more dependent on marrow hyperactivity than are patients with sickle cell anemia.

Addition of erythropoietin — The myelosuppressive effect of HU may compromise its therapeutic efficacy, suggesting the use of erythropoietin to support red cell production when HU is used in the treatment of beta thalassemia. This was tested in a randomized trial in 80 transfusion-dependent subjects ≤18 years of age with thalassemia intermedia (TI). All received HU (25 mg/kg per day by mouth) and were randomly assigned to receive (Group A) or not receive (Group B) recombinant human erythropoietin (EPO, total dose of 1000 international units/kg per week subcutaneously, divided into three doses per week). After a mean follow-up period of one year,

the following results were obtained [95]:

- Subjects receiving both HU and EPO (Group A) had significantly greater increases in hemoglobin (1.6 versus 0.7 g/dL) and HbF (17.0 versus 10.8 percent) over baseline than those receiving HU alone (Group B).
- While all 80 subjects were initially transfusion-dependent, 15 of 40 in Group A (37.5 percent) became transfusion-independent, whereas only 6 of 40 in Group B (15 percent) reached this status.
- No serious adverse events necessitating discontinuation of therapy were seen in either group.

While this proof-of-principle study reported better responses to HU plus EPO in patients with lower initial blood EPO levels, HbF levels >40 percent, or prior splenectomy, larger clinical trials with longer follow-up are needed. Questions to be addressed before recommending use of this regimen include determining those who are most likely to respond as well as overall costs and safety of long-term treatment, such as the side effects of high-dose EPO (eg, thrombosis, reduced survival, bone remodeling) and the development of complications (eg, myelodysplasia, acute leukemia) when HU is given in concert with EPO.

Histone deacetylase inhibitors — The disappointing results obtained with HU in thalassemia have led to a search for other agents capable of increasing the production of HbF. The histone deacetylase inhibitors butyrate and trichostatin A activate gamma globin expression via a p38 mitogen-activating protein kinase (MAPK)-dependent mechanism [96].

Butyric acid analogs — The most promising histone deacetylase inhibitors presently under study are derivatives of butyric acid, including arginine butyrate, sodium phenylbutyrate, and related substances [97-101]. Used alone, these agents are inadequately potent in most patients, except at doses that are potentially toxic or poorly tolerated because of the requirement for prolonged intravenous infusions.

Promising results have been obtained with the use of combination therapy with HU and intermittent pulses of butyric acid compounds [97-99,102,103]. For poorly understood reasons, intermittent pulse therapy appears to increase the potency and sustainability of the hemoglobin switching effect obtained with butyric acid compounds. Whether this or other combination regimens will eventually prove to be therapeutically efficacious remains to be seen.

An orally available short-chain fatty acid derivative of butyric acid (sodium 2,2 dimethylbutyrate, HQK-1001) is well tolerated in normal subjects and has been shown to induce gamma globin expression in experimental settings.

- In a randomized, placebo-controlled phase I/II trial in 21 adult patients with thalassemia intermedia, this agent, given at a dose of 20 mg/kg per day for eight weeks, was shown to be well tolerated and to increase median levels of HbF by 6.6 percent and 0.44 g/dL (4.4 g/L) in eight of nine subjects, and total hemoglobin by a mean of 1.1 g/dL (11 g/L) in four of nine subjects [104].
- Increases in HbF (4.8 percent, 0.32 g/dL in one report and 10.9 percent, 0.96 g/dL in the other) and total hemoglobin (0.47 g/dL and 0.93 g/dL) were noted in two separate studies in a total of 19 patients with thalassemia intermedia who received this agent at a dose of 20 mg/kg per day for 24 weeks [105,106].

It remains to be determined whether the magnitude of these changes is sufficient to reduce long-term complications in these patients.

Kit ligand — In one study, addition of kit ligand, with or without dexamethasone, to cell cultures from patients with beta thalassemia intermedia or beta thalassemia major increased cell proliferation, reduced the percent of apoptotic and dyserythropoietic cells and induced a marked increase of gamma globin synthesis required for the production of HbF [107].

Confirmatory in vivo studies in experimental animal models of thalassemia will be required before such treatment can be considered in human subjects, especially since infusions of kit ligand (stem cell factor, Stemgen) have been associated with potentially severe allergic side effects [108].

Decitabine — The cytosine analog decitabine (5-aza-2'-deoxycytidine), which can deplete DNA methyltransferase and potentially activate gamma globin gene expression, has shown efficacy in short- and long-term trials in increasing HbF and total hemoglobin levels in patients with sickle cell anemia failing to respond to HU. (See "Hydroxyurea and other disease-modifying therapies in sickle cell disease", section on '5-Aza deoxycytidine'.)

The utility of low-dose decitabine (0.2 mg/kg subcutaneously twice per week for 12 weeks) was also studied in a small pilot study in five subjects with beta thalassemia intermedia [109]. This treatment increased total hemoglobin and absolute HbF levels in all five, along with favorable changes in indices of hemolysis. The potential of this approach requires further clinical evaluation. Moreover, the long term toxicity and exact mechanism of action of this agent require further evaluation. This agent is not yet suitable for use except in the setting of a carefully controlled clinical trial.

GENE THERAPY — Even though globin gene expression can be readily manipulated in experimental animals, including murine models of beta thalassemia [110-113], the search for a safe, efficient, and specific targeting vector in humans has been difficult, with limited success to date [114]. The challenges are considerable [80,115,116]. The donor globin gene must be inserted into the pluripotent hematopoietic stem cell, in a fashion that allows its tightly regulated but high level expression only in the red cell lineage and only during the period of terminal erythroblast maturation [117-119].

Many of the sequences flanking the globin genes that are necessary for this regulation have been identified and utilized effectively in animal models [117,120,121]. Experiments in animal models suggest that a significant therapeutic benefit could be achieved if the transferred globin gene is expressed at about 15 percent of the level of the alpha-globin mRNA, with about 20 percent of the erythroid precursors expressing the vector genome [122].

A phase I clinical trial for the treatment of ß-thalassemia major using autologous CD34+ hematopoietic progenitor cells transduced with a lentiviral vector encoding the normal human ß-globin gene (NCT01639690) is in progress [123].

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient information: Thalassemia (The Basics)")

SUMMARY AND RECOMMENDATIONS — Clinical manifestations are profound in patients homozygous for impaired beta globin synthesis (ie, beta thalassemia intermedia and beta thalassemia major) and much less pronounced in heterozygotes (ie, beta thalassemia minor). (See 'Definitions' above.)

- **Beta thalassemia minor (trait)** – Subjects with beta thalassemia minor (beta thalassemia trait) require no specific therapy. Transfusions may be required in pregnant women with symptomatic "physiologic" anemia of pregnancy. (See 'Beta thalassemia minor' above.)
- **Beta thalassemia major** – Subjects with beta thalassemia major are severely affected and will die of their disease unless given appropriate medical attention. (See 'Overview' above.)
    - We recommend that all children with beta thalassemia major receive treatment with a hypertransfusion protocol along with iron chelation therapy (**Grade 1A**). Such treatment should be instituted once the

stigmata of the disease become evident and should be rigorously followed. (See 'Chronic hypertransfusion therapy' above and "Chelation therapy for thalassemia and other iron overload states", section on 'Iron chelation in transfusion-dependent thalassemia'.)

- Appropriately selected subjects (eg, younger age, availability of HLA-matched donor, presence or absence of hepatomegaly/hepatic fibrosis, quality of iron chelation therapy) should be considered for potentially curative hematopoietic cell transplantation. (See "Efficacy of hematopoietic cell transplantation in beta thalassemia major".)
- Care for other complications (need for splenectomy, cardiac monitoring, osteoporosis, supportive measures) are discussed in the text.

- **Beta thalassemia intermedia** – Subjects with beta thalassemia intermedia have clinical complications less severe than those seen in beta thalassemia major, and may not develop the need for any treatment until later in life. Accordingly, all patients should be carefully monitored for development of symptomatic anemia, abnormalities in growth and development, symptomatic splenomegaly, iron overload, and cardiopulmonary complications. (See 'Beta thalassemia intermedia' above.)
  - We suggest institution of red cell transfusions and/or a hypertransfusion/chelation regimen in subjects with disease-related complications (eg, activity limitations, delayed growth and development, early appearance of skeletal changes, progressive marrow expansion) (**Grade 2C**). (See 'Anemia and transfusions' above.)
  - We suggest that splenectomy be avoided in these patients if at all possible; splenectomy should be considered only in those with severe disease-related complications such as growth retardation, poor health, leukopenia, thrombocytopenia, increased transfusion need, or symptomatic splenomegaly (**Grade 2C**). (See 'Splenectomy' above.)

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GRAPHICS

Thalassemia variants which may present as Beta Thalassemia intermedia

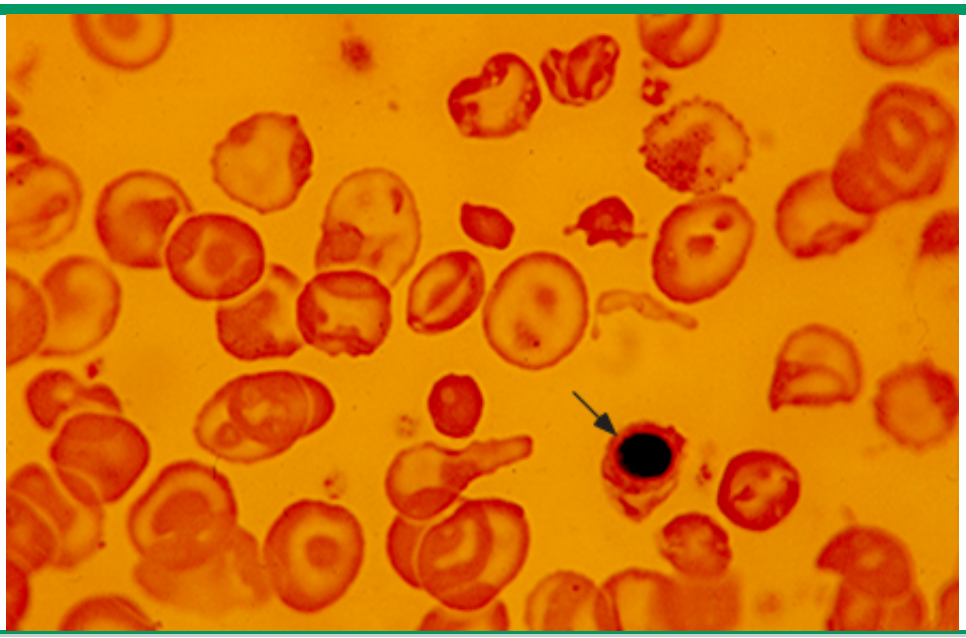
General principles: The pathophysiology of beta thalassemia depends absolutely on the amount of excess unpaired alpha globin chains. Therefore any genetic variant that increases or decreases the amount of these unpaired alpha chains (eg, by altering the rate of alpha or beta chain production, or by substituting for the missing beta chains) will modify the phenotype. Disorders that present as β-thalassemia intermedia, rather than as the major or minor variants, are listed below:
Homozygosity for mild forms of β+ thalassemia
Compound heterozygosity for β+/βº thalassemia
Compound heterozygosity for β thalassemia and another beta chain variant (eg, β-thal/Hgb E)
Coinheritance of homozygous β thalassemia with genes for increased gamma chain synthesis (ie, HPFH)
Coinheritance of homozygous β+ thalassemia with alpha thalassemia (eg, β+/β+ with -a/-a, --/aa, -a/aa, or --/-a)
Coinheritance of heterozygous β thalassemia and triplicated or quadruplicated alpha genes (eg, aa/aaa or aa/aaaa)
Dominant forms of beta thalassemia

β º thalassemia: no production of beta chains; β + thalassemia: reduced production of beta chains (may be mild, moderate, or severely reduced); HPFH: Hereditary persistence of fetal hemoglobin.

Table provided by Stanley L. Schrier, MD.

Graphic 69490 Version 3.0

Peripheral blood smear in beta thalassemia intermedia



Peripheral smear from a patient with beta thalassemia intermedia post-splenectomy. This field shows target cells, hypochromic cells, microcytic cells, red cell fragments, red cells with bizarre shapes, and a single nucleated red cell (arrow).

Courtesy of Stanley Schrier, MD.

Graphic 76666 Version 2.0

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