

Alpha and Beta Thalassemia

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The thalassemias are a group of inherited hematologic disorders caused by defects in the synthesis of one or more of the hemoglobin chains. Alpha thalassemia is caused by reduced or absent synthesis of alpha globin chains, and beta thalassemia is caused by reduced or absent synthesis of beta globin chains. Imbalances of globin chains cause hemolysis and impair erythropoiesis. Silent carriers of alpha thalassemia and persons with alpha or beta thalassemia trait are asymptomatic and require no treatment. Alpha thalassemia intermedia, or hemoglobin H disease, causes hemolytic anemia. Alpha thalassemia major with hemoglobin Bart's usually results in fatal hydrops fetalis. Beta thalassemia major causes hemolytic anemia, poor growth, and skeletal abnormalities during infancy. Affected children will require regular lifelong blood transfusions. Beta thalassemia intermedia is less severe than beta thalassemia major and may require episodic blood transfusions. Transfusion-dependent patients will develop iron overload and require chelation therapy to remove the excess iron. Bone marrow transplants can be curative for some children with beta thalassemia major. Persons with thalassemia should be referred for preconception genetic counseling, and persons with alpha thalassemia trait should consider chorionic villus sampling to diagnose infants with hemoglobin Bart's, which increases the risk of toxemia and postpartum bleeding. Persons with the thalassemia trait have a normal life expectancy. Persons with beta thalassemia major often die from cardiac complications of iron overload by 30 years of age. (*Am Fam Physician*. 2009;80(4):339-344, 371. Copyright © 2009 American Academy of Family Physicians.)

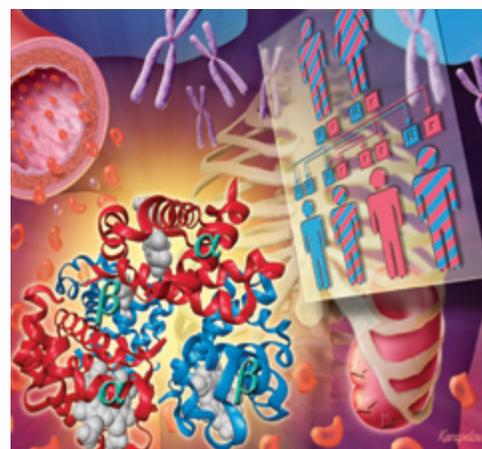


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► **Patient information:** A handout on thalassemia, written by the authors of this article, is provided on page 371.



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The thalassemias (named from the Greek word for sea, *thalassa*¹) are a group of inherited autosomal recessive hematologic disorders² that cause hemolytic anemia because of the decreased or absent synthesis of a globin chain. Imbalances of globin chains cause hemolysis and impair erythropoiesis. Family physicians need to know how to diagnose thalassemias, how to distinguish them from other causes of a microcytic anemia, and the treatment options for severe forms of thalassemia.

Epidemiology

Approximately 5 percent of the world's population has a globin variant, but only 1.7 percent has alpha or beta thalassemia trait.² Thalassemia affects men and women equally and occurs in approximately 4.4 of every 10,000 live births. Alpha thalassemia occurs most often in persons of African and Southeast Asian descent, and beta

thalassemia is most common in persons of Mediterranean, African, and Southeast Asian descent. Thalassemia trait affects 5 to 30 percent of persons in these ethnic groups.²

Pathophysiology

Hemoglobin consists of an iron-containing heme ring and four globin chains: two alpha and two nonalpha. The composition of the four globin chains determines the hemoglobin type. Fetal hemoglobin (HbF) has two alpha and two gamma chains ($\alpha_2\gamma_2$). Adult hemoglobin A (HbA) has two alpha and two beta chains ($\alpha_2\beta_2$), whereas hemoglobin A2 (HbA2) has two alpha and two delta chains ($\alpha_2\delta_2$). At birth, HbF accounts for approximately 80 percent of hemoglobin and HbA accounts for 20 percent.³ The transition from gamma globin synthesis (HbF) to beta globin synthesis (HbA) begins before birth. By approximately six months of age, healthy infants will have transitioned to mostly HbA, a small

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
Persons with anemia from thalassemia trait should not take iron supplements unless they have coexistent iron deficiency.	C	2, 6
Persons with beta thalassemia major require periodic lifelong blood transfusions to maintain hemoglobin levels higher than 9.5 g per dL (95 g per L) and sustain normal growth.	B	2, 15
Persons with beta thalassemia major require chelation therapy for iron overload.	A	16
Persons at risk of having a child with thalassemia should be offered preconception genetic counseling.	C	20, 21

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort.xml>.

amount of HbA₂, and negligible HbF. *Figure 1* shows normal and abnormal hemoglobins.

ALPHA THALASSEMIA

Alpha thalassemia is the result of deficient or absent synthesis of alpha globin chains, leading to excess beta globin chains. Alpha globin chain production is controlled by two genes on each chromosome 16 (*Table 1*^{4,5}). Deficient production is usually caused by a deletion of one or more of these genes. A single gene deletion results in alpha thalassemia silent carrier status, which is asymptomatic with normal hematologic findings. The two-gene deletion causes alpha thalassemia trait (minor) with microcytosis and usually no anemia. The three-gene deletion results in significant production of hemoglobin H (HbH), which has four beta chains (beta₄). Alpha thalassemia intermedia, or HbH disease, causes microcytic anemia, hemolysis, and splenomegaly. The four-gene deletion results in significant production of hemoglobin Bart's (Hb Bart's), which has four gamma chains (gamma₄). Alpha thalassemia major with Hb Bart's usually results in fatal hydrops fetalis.

BETA THALASSEMIA

Beta thalassemia is the result of deficient or absent synthesis of beta globin chains, leading to excess alpha chains. Beta globin synthesis is controlled by one gene on each chromosome 11. Beta thalassemia occurs from any of more than 200 point mutations and (rarely) deletions of the two genes. Beta globin chain production can range from near normal to completely absent, leading to varying degrees of excess alpha globin to beta globin chain production. The one gene defect, beta thalassemia trait (minor), is asymptomatic and results in microcytosis and mild anemia. If the synthesis from both genes is severely reduced or absent, the person has beta thalassemia major, also known as Cooley anemia. Persons with beta thalassemia major are almost never symptomatic at birth because of the presence of HbF, but symptoms begin to develop by six months of age. If the synthesis

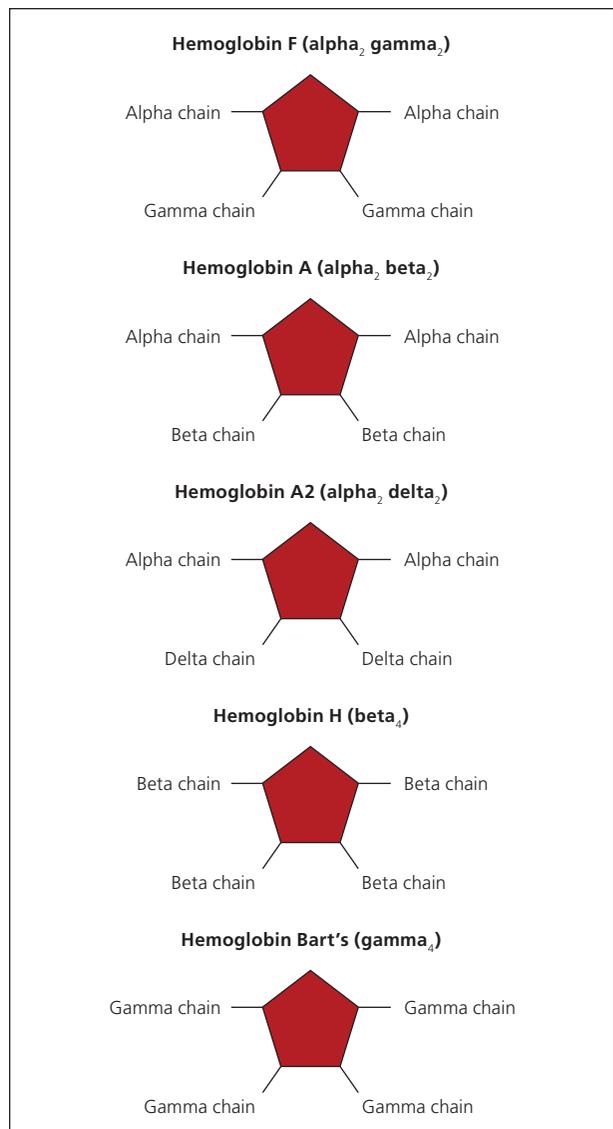


Figure 1. Normal (hemoglobin F, A, and A₂) and abnormal (hemoglobin H and Bart's) hemoglobins. Hemoglobin consists of an iron-containing heme ring and four globin chains: two alpha and two nonalpha. The composition of the four globin chains determines the hemoglobin type.

Table 1. Prototypical Forms of Alpha Thalassemia

<i>Variant</i>	<i>Chromosome 16</i>	<i>Signs and symptoms</i>
Alpha thalassemia silent carrier	One of four gene deletions	Asymptomatic
Alpha thalassemia trait	Two of four gene deletions	Asymptomatic
Hemoglobin Constant Spring	Reduced output of alpha globin	Silent or mildly symptomatic
Alpha thalassemia intermedia with significant hemoglobin H (hemoglobin H disease)	Three of four gene deletions	Moderate to severe hemolytic anemia, modest degree of ineffective erythropoiesis, splenomegaly, variable bone changes ⁴
Alpha thalassemia major with significant hemoglobin Bart's	Four of four gene deletions	Causes nonimmune hydrops fetalis, usually fatal ⁵

Information from references 4 and 5.

of beta chains is less severely reduced, the person has beta thalassemia intermedia. These persons experience symptoms that are less severe and do not require lifelong transfusions to survive past 20 years of age (*Table 2*).⁶

HEMOGLOBINOPATHIES WITH THALASSEMIA

A hemoglobinopathy is a genetic defect that results in an abnormal structure of a globin chain. A thalassemia results in an abnormally low quantity of a globin chain.



Rarely, persons will have coexisting hemoglobinopathy and thalassemia (*Online Table A*).

Diagnosis

Most persons with thalassemia trait are found incidentally when their complete blood count shows a mild microcytic anemia. Microcytic anemia can be caused by iron deficiency, thalassemia, lead poisoning, sideroblastic anemia, or anemia of chronic disease. The mean corpuscular volume (MCV), red blood cell distribution width (RDW), and the patient's history can exclude some of these etiologies. The MCV is usually less than 75 fl with thalassemia and rarely less than 80 fl in iron deficiency until the hematocrit is less than 30 percent. For children, the Mentzer index (MCV/red blood cell count) can help distinguish between iron deficiency and thalassemia. In iron deficiency, the ratio is usually greater than 13,

whereas thalassemia yields values less than 13. A ratio of 13 would be considered uncertain.⁷

The RDW may assist in differentiating iron deficiency and sideroblastic anemia from thalassemia (*Table 3*). The RDW will be elevated in more than 90 percent of persons with iron deficiency, but in only 50 percent of persons with thalassemia.⁸ The RDW is usually elevated in sideroblastic anemia. Therefore, although a microcytic anemia with a normal RDW will almost always be because of thalassemia, persons with an elevated RDW will require additional testing (*Figure 2*).⁹

Supplemental tests include serum ferritin, the peripheral smear, hemoglobin electrophoresis, serum lead level, and rarely bone marrow aspirate. Serum ferritin is the best test to screen for iron deficiency anemia.¹⁰ In the absence of inflammation, a normal ferritin level generally excludes iron deficiency. Serum iron, total iron-binding capacity, and transferrin saturation are rarely needed. Sideroblastic anemia can be excluded with an examination of the peripheral smear or the bone marrow aspirate. A normal serum lead level excludes lead poisoning. Anemia of chronic disease is most often a normocytic normochromic mild anemia. If thalassemia is still suspected, a hemoglobin electrophoresis may help diagnose the condition.

The hemoglobin electrophoresis with beta thalassemia trait usually has reduced or absent HbA, elevated levels

Table 2. Prototypical Forms of Beta Thalassemia

<i>Variant</i>	<i>Chromosome 11</i>	<i>Signs and Symptoms</i>
Beta thalassemia trait	One gene defect	Asymptomatic
Beta thalassemia intermedia	Two genes defective (mild to moderate decrease in beta globin synthesis)	Variable degrees of severity of symptoms of thalassemia major
Beta thalassemia major	Two genes defective (severe decrease in beta globin synthesis)	Abdominal swelling, growth retardation, irritability, jaundice, pallor, skeletal abnormalities, splenomegaly; requires lifelong blood transfusions ⁶

Information from reference 6.

Table 3. Hematologic Indices of Iron Deficiency and Alpha and Beta Thalassemia

Test	Iron deficiency	Beta thalassemia	Alpha thalassemia
MCV (abnormal if < 80 fl in adults; < 70 fl in children six months to six years of age; and < 76 fl in children seven to 12 years of age)	Low	Low	Low
Red blood cell distribution width	High	Normal; occasionally high	Normal
Ferritin	Low	Normal	Normal
Mentzer index for children (MCV/red blood cell count)	> 13	< 13	< 13
Hb electrophoresis	Normal (may have reduced HbA2)	Increased HbA2, reduced HbA, and probably increased HbF	Adults: normal Newborns: may have HbH or Hb Bart's

Hb = hemoglobin; HbF = fetal hemoglobin; MCV = mean corpuscular volume.

of HbA2, and increased HbF.² However, a normal concentration of HbA2 does not rule out beta thalassemia trait, especially if there was coexistent iron deficiency, which can lower HbA2 levels into the normal range. In the newborn period, if the electrophoresis shows Hb Bart's or HbH, the infant has alpha thalassemia. The hemoglobin electrophoresis is usually normal in adults with alpha thalassemia trait.

Persons with beta thalassemia major are diagnosed

during infancy. Pallor, irritability, growth retardation, abdominal swelling, and jaundice appear during the second six months of life.⁶

Persons with a microcytic anemia but milder symptoms that start later in life have beta thalassemia intermedia.

Complications

The complications that occur with beta thalassemia major or intermedia are related to overstimulation of the bone marrow, ineffective erythropoiesis, and iron overload from regular blood transfusions. Untreated infants have poor growth, skeletal abnormalities, and jaundice. Alpha thalassemia intermedia, or HbH disease, causes hemolysis and severe anemia. Alpha thalassemia major with Hb Bart's causes nonimmune hydrops fetalis in utero, which is almost always fatal.

With multiple blood transfusions and continued absorption of intestinal iron, iron overload develops. Iron is deposited in visceral organs (mainly the heart, liver, and endocrine glands), and most patient deaths are caused by cardiac complications.¹¹ Endocrinopathies, particularly hypogonadism and diabetes mellitus, may occur in adolescents and adults.²

Splenomegaly invariably develops in the symptomatic thalassemias. Splenomegaly can worsen the anemia and occasionally cause neutropenia and thrombocytopenia.

Thromboembolic events, venous and arterial, are not uncommon. Persons with beta thalassemia major or intermedia may develop a chronic hypercoagulable state,¹² especially after splenectomy.¹³

Osteopenia and osteoporosis are being found more often as persons with thalassemia major live longer. One study found osteoporosis in 51 percent of persons older than 12 years with thalassemia major.¹⁴

Use of RDW Values in the Diagnosis of Thalassemia

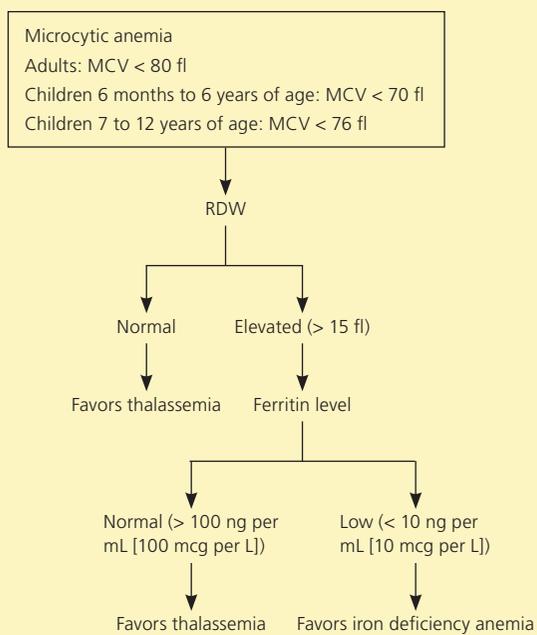


Figure 2. Algorithm of the use of RDW values to assist in diagnosing thalassemia. (MCV = mean corpuscular value; RDW = red blood cell distribution width.)

Information from reference 9.

General Management Issues

Persons with thalassemia trait require no treatment or long-term monitoring. They usually do not have

iron deficiency, so iron supplements will not improve their anemia. Accordingly, iron therapy should only be administered if iron deficiency occurs.^{2,6}

BLOOD TRANSFUSIONS

Persons with beta thalassemia major require periodic and lifelong blood transfusions to maintain a hemoglobin level higher than 9.5 g per dL (95 g per L) and sustain normal growth.^{2,15} The need for blood transfusions may begin as early as six months of age. For persons with beta thalassemia intermedia, the decision to transfuse is a more subjective clinical assessment. Transfusion requirements are episodic and become necessary when the person's hemoglobin is inadequate for a normal life or when the anemia impairs growth and development.

Alpha thalassemia intermedia, or HbH disease, causes mild to moderate hemolysis. Transfusions will occasionally be necessary depending upon the severity of the clinical condition.

CHELATION

Transfusion-dependent patients develop iron overload because they have no physiologic process to remove excess iron from multiple transfusions. Therefore, they require treatment with an iron chelator starting between five and eight years of age.¹⁶ Deferoxamine (Desferal), subcutaneously or intravenously, has been the treatment of choice. Although this therapy is relatively nontoxic, it is cumbersome and expensive. The U.S. Food and Drug Administration recently approved oral deferasirox (Exjade) as an alternative treatment.¹⁷ Adverse effects of deferasirox were transient and gastrointestinal in nature, and no cases of agranulocytosis were reported.

BONE MARROW TRANSPLANT

Bone marrow transplantation in childhood is the only curative therapy for beta thalassemia major. Hematopoietic stem cell transplantation generally results in an excellent outcome in low-risk persons, defined as those with no hepatomegaly, no portal fibrosis on liver biopsy, and regular chelation therapy, or at most, two of these abnormalities.²

Management of Specific Conditions

HYPERSPLENISM

If hypersplenism causes a marked increase in transfusion requirements, splenectomy may be needed. Surgery is usually delayed until at least four years of age because of the spleen's role in clearing bacteria and preventing sepsis. At least one month before surgery, patients should

receive the pneumococcal polysaccharide vaccine. Children should also receive the pneumococcal conjugate vaccine series. Antibiotic prophylaxis with penicillin, 250 mg orally twice a day, is recommended for all persons during the first two years after surgery and for children younger than 16 years.¹⁸

ENDOCRINOPATHIES

Growth hormone therapy for beta thalassemia intermedia and major has had variable success and is not generally recommended. Hormone therapy is effective for hypogonadism.¹⁹

PREGNANCY

Preconception genetic counseling is strongly advised for all persons with thalassemia.²⁰ Two parents, each with beta thalassemia trait, have a one in four chance of conceiving a child with beta thalassemia major and a three in four chance the child will have thalassemia trait or be normal (*Online Figure A*). Persons with alpha thalassemia trait have a more complex pattern of inheritance. Whether both defective genes are on the same  or different chromosomes will alter the outcome (*Online Figure B*).

Chorionic villus sampling using polymerase chain reaction technology to detect point mutations or deletions can identify infants affected with beta thalassemia. Persons with alpha thalassemia trait should consider prenatal diagnosis because Hb Bart's increases the risk of toxemia and postpartum bleeding. Preimplantation genetic diagnosis is becoming available in conjunction with in vitro fertilization.²¹

CARDIAC

Serum ferritin has been used as a marker of iron storage to predict cardiac complications. Ferritin levels less than 2,500 ng per mL (2,500 mcg per L) are associated with improved survival.²² However, ferritin levels are unreliable when liver disease is present.²³

HYPERCOAGULOPATHY

No randomized or observational studies regarding anticoagulation, antiplatelet therapy, or both have been reported for persons at greater risk of thromboembolic events. Therefore, no specific treatment can be recommended. Persons with a history of thrombosis may be treated with low-molecular-weight heparin. Anticoagulation therapy is warranted before surgery and during pregnancy for at-risk persons. Alternatives to estrogen-containing contraception should be offered to women of reproductive age.

Thalassemia

PSYCHOSOCIAL

Beta thalassemia major or intermedia is a chronic disease with a significant impact on the patient and the patient's family and offspring. Education about the genetics of the disease, prenatal diagnosis options, and psychological therapy to help manage the complications is appropriate. However, neither the type of education nor the duration of therapy can be specified based on current evidence.²⁴

VITAMIN DEFICIENCIES

Folic acid deficiency has been reported in thalassemia major and intermedia as a result of increased erythropoiesis. Therefore, daily oral supplementation with 1 mg of folic acid is recommended for persons with evidence of folate deficiency.¹⁸

Because some complications seem to be related to cellular oxidative stress, treatment with antioxidants has been thought to be beneficial.¹⁸ However, no improvements in anemia or reductions in morbidity or mortality have been demonstrated. Vitamin C is not recommended except in transfusion-dependent patients with a proven deficiency.

Prognosis

Persons with thalassemia trait have a normal life expectancy. Persons with beta thalassemia major live an average of 17 years and usually die by 30 years of age. Most deaths are caused by the cardiac complications of iron overload.¹¹

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REFERENCES

1. Whipple GH, Bradford WL. Mediterranean disease: thalassemia (erythroblastic anemia of Cooley). *J Pediatr*. 1936;9:279-311.

- Rund D, Rachmilewitz E. Beta-thalassemia. *N Engl J Med*. 2005;353(11):1135-1146.
- Richardson M. Microcytic anemia [published corrections appear in *Pediatr Rev*. 2007;28(4):151, and *Pediatr Rev*. 2007;28(7):275]. *Pediatr Rev*. 2007;28(1):5-14.
- Chui DH, Fucharoen S, Chan V. Hemoglobin H disease: not necessarily a benign disorder. *Blood*. 2003;101(3):791-800.
- Chui DH, Wray JS. Hydrops fetalis caused by alpha-thalassemia: an emerging health care problem. *Blood*. 1998;91(7):2213-2222.
- Olivieri NF. The beta-thalassemias [published correction appears in *N Engl J Med*. 1999;341(18):1407]. *N Engl J Med*. 1999;341(2):99-109.
- Mentzer WC Jr. Differentiation of iron deficiency from thalassaemia trait. *Lancet*. 1973;1(7808):882.
- Flynn MM, Reppun TS, Bhagavan NV. Limitations of red blood cell distribution width (RDW) in evaluation of microcytosis. *Am J Clin Pathol*. 1986;85(4):445-449.
- Marsh WL Jr, Bishop JW, Darcy TP. Evaluation of red cell volume distribution width (RDW). *Hematol Pathol*. 1987;1(2):117-123.
- Guyatt GH, Oxman AD, Ali M, Willan A, McIlroy W, Patterson C. Laboratory diagnosis of iron-deficiency anemia: an overview [published correction appears in *J Gen Intern Med*. 1992;7(4):423]. *J Gen Intern Med*. 1992;7(2):145-153.
- Modell B, Khan M, Darlison M. Survival in beta-thalassaemia major in the UK: data from the UK Thalassaemia Register. *Lancet*. 2000;355(9220):2051-2052.
- Eldor A, Rachmilewitz EA. The hypercoagulable state in thalassemia. *Blood*. 2002;99(1):36-43.
- Cappellini MD, Robbiolo L, Bottasso BM, Coppola R, Fiorelli G, Mannucci AP. Venous thromboembolism and hypercoagulability in splenectomized patients with thalassaemia intermedia. *Br J Haematol*. 2000;111(2):467-473.
- Jensen CE, Tuck SM, Agnew JE, et al. High prevalence of low bone mass in thalassaemia major. *Br J Haematol*. 1998;103(4):911-915.
- Cazzola M, Borgna-Pignatti C, Locatelli F, Ponchio L, Beguin Y, De Stefano P. A moderate transfusion regimen may reduce iron loading in beta-thalassemia major without producing excessive expansion of erythropoiesis. *Transfusion*. 1997;37(2):135-140.
- Roberts DJ, Brunskill SJ, Doree C, Williams S, Howard J, Hyde CJ. Oral deferiprone for iron chelation in people with thalassaemia. *Cochrane Database Syst Rev*. 2007;(3):CD004839.
- Deferasirox (Exjade): a new iron chelator. *Med Lett Drugs Ther*. 2006;48(1233):35-36.
- Borgna-Pignatti C. Modern treatment of thalassaemia intermedia. *Br J Haematol*. 2007;138(3):291-304.
- De Sanctis V. Growth and puberty and its management in thalassaemia. *Horm Res*. 2002;58(suppl 1):72-79.
- ACOG Committee on Obstetrics. ACOG practice bulletin no. 78: hemoglobinopathies in pregnancy. *Obstet Gynecol*. 2007;109(1):229-237.
- Braude P, Pickering S, Flinter F, Oglivie CM. Preimplantation genetic diagnosis [published correction appears in *Nat Rev Genet*. 2003;4(2):157]. *Nat Rev Genet*. 2002;3(12):941-953.
- Hoffbrand AV, Cohen A, Hershko C. Role of deferiprone in chelation therapy for transfusional iron overload. *Blood*. 2003;102(1):17-24.
- Brittenham GM, Cohen AR, McLaren CE, et al. Hepatic iron stores and plasma ferritin concentration in patients with sickle cell anemia and thalassemia major. *Am J Hematol*. 1993;42(1):81-85.
- Anie KA, Massaglia P. Psychological therapies for thalassaemia. *Cochrane Database Syst Rev*. 2001;(3):CD002890.