Clinical manifestations and diagnosis of the thalassemias

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INTRODUCTION — The major hemoglobin in adults is hemoglobin A, a tetramer consisting of one pair of alpha globin chains and one pair of beta globin chains. In normal subjects, globin chain synthesis is very tightly controlled, such that the ratio of production of alpha to non-alpha chains is 1.00 ± 0.05. Thalassemia refers to a spectrum of diseases characterized by reduced or absent production of one or more globin chains, thus disrupting this closely regulated ratio. (See "Molecular pathology of the thalassemic syndromes".)

- The vast majority of adult patients with alpha or beta thalassemia **minor** are asymptomatic and may be diagnosed because of the presence of microcytic, hypochromic red cells, with or without minor degrees of anemia.
- Thalassemias of intermediate degrees of severity (**thalassemia intermedia**) are common throughout the world, and may be due to the presence of more than one hemoglobin mutation in the same patient (eg, sickle cell thalassemia, hemoglobin E/beta thalassemia) or to the presence of an abnormal hemoglobin with a reduced (ie, thalassemic) production rate (eg, hemoglobin Lepore, hemoglobin Constant Spring).
- Beta thalassemia **major** and alpha thalassemia **major** are on the other end of this spectrum. The former is associated with life-long transfusion-dependent anemia, while the latter is incompatible with extra-uterine life.

The clinical manifestations and diagnosis of the thalassemias will be reviewed here [1]. The management of beta thalassemia is discussed separately. (See "Treatment of beta thalassemia" and "Efficacy of hematopoietic cell transplantation in beta thalassemia major".)

BETA THALASSEMIA MAJOR

Overview — Beta thalassemia is due to impaired production of beta globin chains, leading 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 (ie, beta thalassemia major) and much less pronounced in heterozygotes, who generally have minimal or mild anemia and no symptoms. (See "Pathophysiology of beta thalassemia".)

Infants with severe beta thalassemia major (BTM) are well at birth, because the production of beta globin is not essential during fetal life or the immediate perinatal period. The major non-alpha globin produced at the time of birth is gamma globin, such that the major hemoglobin in early postnatal life is fetal hemoglobin (Hb F, alpha2/gamma2).

Symptoms emerge during the second six months of life when gamma globin chain production decreases and is normally replaced with the production of beta globin to form adult hemoglobin (Hb A, alpha2/beta2). However, since

newborns with BTM are unable to produce beta chains, they develop chronic anemia, the stigmata of profound hemolysis, and suffer the noxious effects of massive ineffective erythropoiesis upon the body. The clinical expression of the severe phenotype is remarkably heterogeneous, depending upon a variety of factors that alter the burden of alpha-globin inclusions in the individual patient [2-6].

When BTM becomes clinically apparent during the second six months of life, pallor, irritability, growth retardation, abdominal swelling due to hepatosplenomegaly, and jaundice reflect the onset and sequelae of severe hemolytic anemia. The symptoms associated with ineffective erythropoiesis (eg, bony abnormalities and abnormal skeletal development) soon follow. Eighty percent of untreated children will die within the first five years of life, due directly to the consequences of severe anemia, high output heart failure, inanition, and unusual susceptibility to infection [4,7,8].

The clinical features outlined below describe the most severe manifestations of BTM, most of which are rarely seen in the United States or other countries with highly developed medical care systems [3]. (See "Community public health issues and the thalassemic syndromes: Lessons from other countries".)

The clinical manifestations of BTM are multifactorial. Even though the primary genetic defect resides in a single gene (ie, beta globin) expressed only during terminal maturation of red cell progenitors, many organ systems are affected. Understanding of the symptomatology of BTM requires recognition that patients suffer simultaneously from the following:

- The effects of severe and chronic anemia
- The stigmata of chronic hemolysis
- Organ damage from transfusional iron overload
- The profound local and systemic effects of a rapidly and relentlessly expanding mass of erythroid bone marrow progenitors

The application of modern forms of hypertransfusion therapy, which can suppress many of the adverse effects of anemia and extramedullary hematopoiesis; marked reduction in the risk of transfusion-associated hepatitis; rigorous use of iron chelation to reverse transfusion-related iron overload; and the use of hematopoietic cell transplantation have ameliorated most of these features [9].

However, in many areas of the world where genetic counseling and/or intensive therapy are not available, patients with severe symptoms are still encountered. Indeed, management of the iron stores in these patients has become the overriding challenge, since most of the manifestations of anemia and hemolysis can be controlled by aggressive hypertransfusion regimens. (See "Iron overload syndromes other than hereditary hemochromatosis", section on 'Transfusional iron overload'.)

Clinical manifestations — The direct effects of BTM on other organs and tissues in the body are due to the deleterious effects of the profound anemia, the byproducts of hemolysis, and the intramedullary and extramedullary expansion of erythroid marrow progenitors [2,4-6,10]. However, in actual practice, patients exhibit both direct and indirect abnormalities of a number of organ systems. Indirect effects include the accumulation of end-organ damage due to iron overload either from blood transfusions or accelerated iron turnover [11], blood-borne infections (eg, viral hepatitis from blood transfusions), or progressive diversion of caloric resources to bone marrow expansion.

Skeletal changes — Skeletal abnormalities are dramatic in these patients and frequently lead to marked changes in the facial structure and body habitus, producing the characteristic "chipmunk facies" and delayed skeletal maturation. Skeletal changes are due largely to the expansion and invasion of erythroid bone marrow, which widen the marrow spaces, attenuate the cortex, and produce osteoporosis.

The skull and facial bones are strikingly abnormal. Marrow expansion causes dramatic widening of the diploic spaces and produces a characteristic "hair-on-end" radiographic appearance of the skull [12]. In addition, there is prominent frontal bossing, delayed pneumatization of the sinuses, and marked overgrowth of the maxillae. As a result, the upper incisors are "jumbled" and the malar eminences are especially prominent, producing malocclusion

and the characteristic facies.

The ribs and the bones of the extremities become box-like and eventually convex, due to expansion of the bone marrow. Premature fusion of the epiphyses can result in characteristic shortening of the limbs, particularly the arms. Of equal concern is the thinning of the cortices due to marrow expansion, which often results in pathologic fractures. Compression fractures of the spine, often with spinal cord compression and neurologic deficits, have been reported in these children.

As children reach the end of the first decade of life, the greatly expanded hematopoietically active ("red") marrow is replaced at the periphery of the skeleton by inactive ("yellow") marrow as in unaffected preadolescent children. The changes in the hands and feet thus become somewhat less prominent in the second decade of life if the child survives. However, changes in the pelvis, skull, and spine become more pronounced, due to the continuation of active erythropoiesis at these sites. It is often in the second decade of life, not surprisingly, that compression fractures and paravertebral expansion of extramedullary masses become particularly prominent. These changes may lead to complications such as back pain, spinal asymmetry and scoliosis, cord compression from intraspinal collections of hematopoietic tissue, and intervertebral disc degeneration [13].

Osteopenia with cortical thinning, increased trabeculation of the spine, severe osteoporosis with fractures, including vertebral fractures in adolescents and young adults, remain serious complications, even in well-transfused and iron-chelated patients [14-16]. The mechanism(s) underlying this observation are unclear. Different studies have identified the following possible contributing factors [13,17-23]:

- The Sp1 polymorphism of the COLIA1 collagen gene, which may predispose to vertebral osteoporosis [17] (see "Pathogenesis of osteoporosis", section on 'Genetics')
- Increased bone resorption that may be related to vitamin D deficiency of uncertain etiology [18,19] (see 'Endocrine and metabolic abnormalities' below). Bone formation may not be impaired [20].
- Failure to progress normally through puberty [21], most likely secondary to hypogonadism [20,22] (see 'Endocrine and metabolic abnormalities' below)
- A direct effect of iron overload on bone, possibly due to iron-induced oxidative stress [24] or activation of osteoclasts [25]
- A direct toxicity of deferoxamine, leading to skeletal dysplasia [26,27]
- Zinc deficiency [28-30] (see 'Vitamin and mineral levels' below)

Liver and gallbladder — Hepatomegaly is prominent early in the disease, due to increased red cell destruction as well as extramedullary erythropoiesis in this organ. Liver enlargement tends to be somewhat more prominent in children with BTM than in others with other causes for congenital hemolytic anemia. Later in the first decade of life, hepatomegaly becomes fixed and not reducible by blood transfusion, due to development of cirrhosis secondary to increased iron deposition.

Even in the absence of transfusion, the accelerated rate of erythropoiesis enhances dietary iron absorption from the gut, resulting in a chronic state of iron overload. In the liver, iron first infiltrates Kupffer cells and then engorges hepatocytes, ultimately provoking fibrosis and, potentially, end-stage liver disease, in a manner analogous to that seen in hereditary hemochromatosis.

A curious feature of deranged iron homeostasis in individuals with BTM is that hepcidin levels remain low despite massive iron overload [31]. Such reduced hepcidin production enhances the absorption of iron from the diet, increasing the already high iron burden. Serum from thalassemic subjects blocks hepcidin synthesis in cultured liver cells [32], suggesting that thalassemic serum contains a circulating repressor of hepcidin [33]. (See "Iron overload syndromes other than hereditary hemochromatosis", section on 'Anemia due to ineffective erythropoiesis' and "Regulation of iron balance", section on 'Hepcidin'.)

Liver changes consistent with viral hepatitis, both hepatitis B and hepatitis C, are frequent, even in children who have received little or no transfusion therapy. While hepatitis as a complication of transfusion is readily understandable, the prevalence in non-transfused children suggests additional susceptibility factors. Iron overload is one situation thought to favor susceptibility to viral hepatitis.

In view of the above, it is not surprising that liver function abnormalities are highly prevalent, but variable, given the multiplicity of underlying causes. Hyperbilirubinemia is nearly universal. Most affected children also have hypergammaglobulinemia and abnormal hepatocellular enzyme markers. In advanced stages of the disease, probably as the result of hemochromatosis and exposure to hepatitis B and C viruses through multiple blood transfusions, hypoalbuminemia, coagulation factor abnormalities, and other stigmata of end-stage liver disease (eg, hepatocellular carcinoma) may appear [34].

A prominent feature of children with chronic hemolytic anemia is the development of premature bilirubin gallstone disease and biliary tract inflammation. This is particularly true of children with BTM. Two-thirds of these patients have multiple calcified bilirubin stones by the age of 15 [35]. Fortunately, true episodes of cholecystitis or cholangitis are rare. Gall bladder removal is thus rarely indicated in the absence of clear-cut symptoms.

Splenomegaly — Massive splenomegaly develops early in the course of BTM due to increased red cell destruction and the presence of splenic extramedullary hematopoiesis. Splenomegaly is progressive and can produce characteristic symptoms such as early satiety and hypersplenism. Shortened survival of transfused red cells or progressive worsening of the anemia or other cytopenias in non-transfused patients are indications that removal of the spleen may palliate symptoms by reducing splenic consumption of red cells. However, children often require splenectomy whether or not they are transfused. (See "Extrinsic nonimmune hemolytic anemia due to mechanical damage: Fragmentation hemolysis and hypersplenism", section on 'Extravascular nonimmune hemolysis due to hypersplenism'.)

Before and after splenectomy, children with BTM suffer immune deficits as the result of premature loss of splenic function [2]. Splenic monocytes and macrophage are particularly important for clearance of bacteria and other particulate matter, and splenic leukocytes appear to be important in early life for the maturation of the alternative pathway of complement activation. Iron overload within the spleen and engorgement of splenic reticuloendothelial cells are both thought to contribute to abnormal splenic function, even when the spleen is anatomically present.

Splenectomy — If splenectomy is performed, children with BTM, like all other splenectomized patients, are at considerable risk for overwhelming sepsis. Vaccination against pneumococcus and prophylactic use of antibiotics are essential. (See "Prevention of sepsis in the asplenic patient".)

Patients with BTM or thalassemia intermedia may also be at increased risk for developing thromboembolic phenomena, including stroke, following splenectomy [36-38].

Kidneys — The kidneys are frequently enlarged in thalassemia, due to the presence of extramedullary hematopoiesis. Less well understood is the tendency for the renal tubules to be dilated. The urine is frequently dark, due to increased concentrations of bile pigments; large amounts of urate, uric acid, and oxalate are also seen.

Because of the high rate of cellular turnover in this disease, hyperuricemia is encountered in children with BTM, and they are at risk for development of gouty nephropathy. However, true attacks of gouty arthritis are rare before the second or third decade of life. (See "Asymptomatic hyperuricemia".)

Endocrine and metabolic abnormalities — Endocrine and metabolic abnormalities are quite common in patients with BTM, attributable, at least in part, to chronic iron overload [39]. In a study of 56 patients with transfusional iron overload (52 with either thalassemia major or intermedia), pituitary iron overload was detected by magnetic resonance imaging during the first decade of life, while clinically significant pituitary volume loss was not observed until the second decade of life [40]. Both pituitary iron overload and volume loss were independently predictive of hypogonadism, which was defined clinically based upon the timing of secondary sexual characteristics

or the need for sex hormone replacement therapy.

In two studies comprising over 800 patients with transfusion-dependent thalassemia, the following endocrine/metabolic abnormalities were noted [39,41]:

- Hypogonadism – 40 to 55 percent
- Growth failure – 33 percent
- Diabetes – 6 to 13 percent
- Hypothyroidism – 10 to 11 percent

There is increasing evidence that chelation therapy can arrest the **progression** of these endocrine abnormalities [41-45]. However, it is not yet entirely clear whether actual **reversal** of endocrine dysfunction can be achieved by chelation. At least one report suggests that intensive chelation therapy with two agents (eg, deferoxamine plus deferiprone) might accomplish this latter goal [46]. (See "Chelation therapy for thalassemia and other iron overload states".)

Growth retardation is frequently profound in these children. This reflects, in part, the diversion of caloric resources for erythropoiesis, along with the effects of anemia, since hypertransfusion frequently restores growth rates to normal. However, the adolescent growth spurt is often delayed, even in children who are hypertransfused, unless intensive iron chelation therapy is instituted early in life.

Primary and secondary characteristics of sexual development are usually delayed for both boys and girls [22]. While there is increasing evidence that hypogonadism may be primarily due to iron overload, zinc deficiency may also play a role.

- Menarche is frequently delayed, breast development is often poor, and patients are frequently oligomenorrheic or amenorrheic, even if menarche occurs.
- Boys frequently develop no or sparse facial and body hair and tend to have decreased libido, even if sperm production does occur.

A report from the Thalassemia Clinical Research Network reported on the following findings in 361 subjects with thalassemia (mean age 23, range: 6 to 75 years) living in North America and receiving current therapy [47]:

- Approximately 25 percent of children and adults, regardless of their thalassemia syndrome, had short stature. Overall growth in children was mildly affected and final height was close to midparental height.
- Patients with beta thalassemia major had higher rates of multiple endocrinopathies, worse hyperglycemia, subclinical hypoparathyroidism, and hypercalciuria. All were found to correlate with higher ferritin concentrations.
- Hypogonadism, the most frequent endocrinopathy, was frequently undertreated. Among hypogonadal girls, menarche was delayed to 17 years.
- Low levels of vitamin D were common, especially among adolescents.

Diabetes mellitus — Abnormal carbohydrate metabolism is another major endocrine abnormality encountered in these children [48]. Glucose intolerance usually develops during the second decade of life, even though baseline blood sugar levels are frequently normal. Interestingly, the early lesion appears to be related more to insulin resistance than to defective insulin production. The latter is a complication that occurs only during the late stages of development of hemosiderosis. More effective iron chelation appears to improve glucose intolerance [49].

A retrospective historical study evaluated the incidence of diabetes mellitus (DM) in 957 patients with BTM as well as the effect of DM on cardiac complications. Results included the following [50]:

- The incidence of DM in this population was 9 percent. When compared with those without DM, patients with BTM and DM were older, had started chelation at an older age, and had a higher incidence of endocrine co-

morbidity (eg, hypogonadism, hypothyroidism, hypoparathyroidism).

- Although there were no significant differences between DM and non-DM patients for global cardiac T2*, those with DM had significantly increased frequencies of heart failure, hyperkinetic (atrial) arrhythmias, and myocardial fibrosis.

These results are concordant with the increased vulnerability in the general population of the diabetic heart to failure and arrhythmia, and are relevant for the prevention of disorders of glucose metabolism, particularly in young patients. They also stress the need to intensify chelation therapy in patients with BTM in whom excess pancreatic iron is found by MRI (where available) and/or when such patients develop disorders of glucose metabolism, since improvement is possible with enhanced chelation therapy [49]. (See "Heart failure in diabetes mellitus", section on 'Epidemiology'.)

Cardiac complications — Cardiac abnormalities are a major feature of BTM [51,52]. Cardiac malfunction, including heart failure and fatal arrhythmias, are frequent causes of death, and cardiac dilatation secondary to anemia is nearly universal. Transfusion usually corrects the latter abnormality, but may lead to cardiac hemosiderosis due to myocardial iron deposition. Cardiomegaly, non-specific electrocardiographic changes (eg, bradycardia, repolarization abnormalities), and atrial as well as left ventricular dysfunction ensue in the untreated child [53-56], leading to end-stage cardiomyopathy. (See "Clinical utility of cardiovascular magnetic resonance imaging", section on 'Iron overload'.)

Additional risk factors for the development of cardiovascular complications may include:

- Vascular endothelial dysfunction and increased arterial stiffness have been found in children with hemoglobin E beta thalassemia despite treatment with periodic blood transfusions and iron chelation therapy, and have been attributed, at least in part, to the presence of oxidative stress markers and increased levels of non transferrin bound iron [57].
- Presence of the epsilon-4 allele of apolipoprotein E [58], which has decreased antioxidant and iron-binding activity compared with the epsilon-2 and epsilon-3 alleles [59].
- Presence of the null (deleted) genotype for glutathione S-transferase M1, an enzyme which, when present, may help reduce some of the oxidant damage due to increased iron deposition in tissues [60].
- A relationship among vitamin D deficiency, cardiac iron uptake, and ventricular dysfunction has been suggested, although the mechanism involved is not clear [61].
- In an MRI-based study, there was a significant incidence of myocardial fibrosis/necrosis, correlating best with presence of cardiovascular risk factors, a history of cardiac complications, and anti-HCV antibodies, rather than myocardial iron overloading [62].
- In a study of135 transfusion-dependent patients with beta thalassemia, 18 (13 percent) satisfied MRI criteria for the rare cardiomyopathy left ventricular noncompaction (LVNC) [63]. There were no statistically significant differences between patients with and without LVNC with respect to demographics, hemoglobin levels, splenectomy status, iron overload status, liver disease, infection, or iron chelator type. (See "Isolated left ventricular noncompaction".)

In transfused patients with BTM, cardiac hemosiderosis is the most feared complication. Without early institution of iron chelation therapy, a characteristic cardiomyopathy due to iron overload develops. These patients develop a sterile pericarditis, arrhythmias (both supraventricular and ventricular), poor exercise performance [64], and end-stage restrictive cardiomyopathy leading to heart failure [55,65,66].

Fatal ventricular arrhythmias are a frequent cause of death. Rhythm disturbances begin with the characteristic prolongation of the PR interval, then first degree heart block, premature atrial beats, and, later, ST segment depression and ventricular ectopy.

Magnetic resonance imaging — Cardiovascular magnetic resonance imaging (MRI) is considered the "gold standard" for measurement of all left and right ventricular indices, while myocardial iron deposition can be quantified reproducibly with myocardial T2*, a relaxation parameter that arises on MRI principally from local magnetic field inhomogeneities that are increased with iron deposition [55]. (See "Clinical utility of cardiovascular magnetic resonance imaging", section on 'Iron overload' and "Treatment of beta thalassemia", section on 'Cardiac monitoring'.)

The importance of T2* cardiovascular MRI for determining myocardial iron loading and the development of heart failure and cardiac death in transfused patients with BTM was demonstrated in an international survey of 3095 patients in 27 worldwide centers. Results included the following [67]:

- At first scan, 20.6 percent had severe myocardial iron loading (T2* ≤10 ms), 22.8 percent had moderate myocardial iron loading (T2* 10 to 20 ms), and 56.6 percent had no iron loading (T2* >20 ms).
- At first scan, 85 of 2915 patients (2.9 percent) were reported to have heart failure. Of these, 81 percent had a T2* <10 ms and 99 percent had a T2* <20 ms.
- During follow-up, 108 of 2830 patients (3.8 percent) developed new heart failure. Of these, T2* at first scan had been <10 ms in 96 percent and <20 ms in 100 percent.
- There were 35 cardiac deaths (1.1 percent). Of these, T2* at first scan had been <10 ms in 86 percent and <20 ms in 97 percent.

Ninety-seven percent of those undergoing their first T2* scan in this report were taking regular iron chelation, and 93 percent had been taking iron chelation therapy for more than five years. Since a cardiac T2* <20 ms, which was present in over 40 percent of the subjects in this study, indicates inadequate chelation, issues such as compliance and intensification of treatment must be addressed in all patients with BTM undergoing iron chelation therapy [68]. (See "Chelation therapy for thalassemia and other iron overload states", section on 'Overall goals of iron chelation therapy'.)

Pulmonary complications — For poorly understood reasons, most patients with BTM have mild abnormalities of pulmonary function, including restrictive and small airway obstructive defects, hyperinflation, decreased maximal oxygen uptake, and abnormal anaerobic thresholds. These abnormalities are not corrected by transfusion and do not correlate with somatic iron burden, blood counts, or hemolysis [69]. After splenectomy, profound thrombocytosis places these patients at risk for pulmonary vascular obstruction.

Pulmonary hypertension — Although primary pulmonary symptoms are relatively infrequent in thalassemia, adult patients may develop pulmonary hypertension (PAH), the cause of which is not entirely clear [70], but may be related to such factors as prior splenectomy, older age, chronic hemolysis, iron overload, platelet activation, and smoking [71-74]. (See "Pulmonary hypertension associated with sickle cell disease", section on 'Introduction'.)

As an example, in a multicenter cross-sectional study of 1309 patients with beta thalassemia, those with a tricuspid valve regurgitant jet velocity ≥3.2 m/sec on transthoracic echocardiography underwent right heart catheterization to confirm the diagnosis of PAH (mean pulmonary arterial pressure ≥25 mmHg and pulmonary capillary wedge pressure ≤15 mmHg). Results included the following [74]:

- The positive predictive value for a tricuspid valve regurgitant jet velocity ≥3.2 m/sec threshold for the diagnosis of PAH was 94 percent. The confirmed PAH prevalence on right heart catheterization was 2.1 percent (95% CI 1.4-3.0) and was four times higher in those with thalassemia intermedia than in those with thalassemia major (4.8 versus 1.1 percent).
- Considerable functional limitation and decrease in the six-minute walk distance were noted in patients with confirmed PAH. On multivariate analysis, independent risk factors for confirmed PAH were increasing age (OR 1.1 per one-year increase) and prior splenectomy (OR 9.3; 95% CI 2.6-34).

Aplastic crisis — Parvovirus B19 infects erythroid precursor stem cells. In normal children, this results in a very mild transient erythrocytopenia because the impairment of marrow function is transitory and the 120-day survival of normal red blood cells protects them from acute drops in the red cell count. (See "Clinical manifestations and diagnosis of human parvovirus B19 infection".)

In patients with extremely shortened red cell survival, as in BTM, the effect is far more profound. These patients depend on very high rates of red cell production; moreover, the shortened red cell survival (four to eight days) causes the red cell count to fall rapidly when production is stopped. Children with BTM who develop B19 infection thus develop dramatic, often life threatening drops in hematocrit with reticulocyte counts of nearly zero. This "aplastic crisis" often requires emergent transfusion support [2,4].

Milder decreases in rates of red cell production frequently accompany other infections (hypoplastic crises), probably due to the amplified effects of the short red cell survival on transient partial suppression of erythropoiesis occurring in association with infection.

Chronic pain — A multicenter prospective study of 258 thalassemia patients (mean age 29; range 12 to 71) receiving care at 12 Thalassemia Clinical Research Network sites has revealed that 81 percent reported having pain for ≥1 year, and 31 percent reported pain for ≥5 years [75]. Patients with pain reported an average number of four sites of pain, which included the lower back (82 percent), leg (56 percent), head (48 percent), and midback (47 percent). Of those questioned about pain during the prior four-week period, 36 percent had no pain, while it was considered mild, moderate, or severe in 36, 19, and 9 percent, respectively. Regression analysis demonstrated a significant correlation of increased age with increased pain, irrespective of the type of thalassemia, transfusion status, gender, bone density, chelator type, or degree of iron overload. Although this pain syndrome appears to be a major cause of morbidity [76], its etiology and predictors remain unexplained.

Laboratory findings

Red blood cells — Profound hypochromic, microcytic anemia accompanied by bizarre red cell morphology is a hallmark of beta thalassemia major (BTM) [2,3]. The hemoglobin level may be as low as 3 to 4 g/dL. Red cell morphology is dramatically abnormal in most patients, with extreme hypochromia and poikilocytosis, a predominance of microcytes, tear drop and target cells (picture 1), and the visibility, even in routine stains, of clumped inclusion bodies representing precipitates of alpha globin within the red cell. These precipitates (Heinz bodies) can be more readily appreciated by staining with methyl violet or other supravital stains.

The white blood cell (WBC) count is often strikingly high, and the reticulocyte count surprisingly low. The latter reflects the severe degree of ineffective erythropoiesis underlying the disorder, resulting in many fewer than the expected number of reticulocytes being released from the bone marrow. The high white count may be misleading, since these patients release many nucleated red blood cells (NRBC) into the peripheral blood. Depending on the counting method used, NRBC can be miscounted as leukocytes. However, even when corrected for this phenomenon, a true neutrophilia is often encountered.

The platelet count is usually normal. However, hypersplenism can lower both white cell and platelet counts. Splenectomy usually produces exaggerated rises in circulating NRBC, WBC, and platelets in the peripheral blood. (See 'Splenomegaly' above.)

Iron studies — Because of the high rate of erythroid cell turnover, the serum iron level is usually elevated; the transferrin saturation, expressed as the ratio of serum iron to total iron binding capacity (or transferrin), is very high [2].

Serum ferritin levels in those with thalassemia major may be quite elevated, reflecting the presence of iron overload primarily from multiple blood transfusions, but to a lesser extent from increased absorption of dietary iron from the gastrointestinal tract. (See "Iron overload syndromes other than hereditary hemochromatosis", section on 'Anemia due to ineffective erythropoiesis' and "Iron overload syndromes other than hereditary hemochromatosis", section on 'Transfusional iron overload'.)

Other laboratory studies — The serum is often icteric; increased concentrations of indirect (unconjugated) bilirubin and lactate dehydrogenase, and low levels of haptoglobin, findings typical of hemolytic disease, are usually present. (See "Approach to the diagnosis of hemolytic anemia in the adult".)

Vitamin and mineral levels — Vitamin and mineral levels relevant to bone marrow homeostasis, such as folate, vitamin B12, and pyridoxine, are usually normal.

- Folate deficiency can develop in these patients, due to the high rate of cellular turnover.
- Serum zinc levels tend to be particularly low in these patients, likely due to increased requirements for this essential element and/or increased excretion subsequent to the use of iron chelating agents [28,77-79].
- Serum and leukocyte ascorbic acid levels are reduced, possibly as a result of accelerated catabolism in the face of iron overload. Serum levels of vitamin E are also sometimes low, perhaps for the same reasons.

Bone marrow examination — Bone marrow examination reveals profound erythroid hyperplasia that is unusual for the degree of immaturity and bizarre morphology of the erythroid progenitors. Early erythroblasts are abundant, and often appear megaloblastic, likely reflecting limited supplies of folate and other nutrients. Later erythroid progenitors are less abundant than expected, due to their intramedullary destruction (ie, ineffective erythropoiesis), producing a marked "left shift" that was erroneously interpreted as leukemic in the late 19th and early 20th century descriptions of this disease. Alpha globin inclusions are readily apparent, particularly if supravital dyes are used.

Extramedullary hematopoiesis — A dramatic abnormality of the bone marrow, rarely seen in other forms of chronic anemia, is extramedullary erythropoiesis. In the most severely symptomatic children, erythroid bone marrow may invade the bony cortex and break through bone, setting up masses of ectopic erythroid cell colonies in the thoracic or pelvic cavities or sinuses (image 1). These expanding masses can behave clinically like tumors, causing spinal cord compression and other abnormalities [80].

Hemoglobin electrophoresis patterns — Patients with homozygous beta (0) thalassemia are unable to make any Hb A. In untransfused patients only Hb F and Hb A2 are present on hemoglobin electrophoresis. When transfused, they will have variable amounts of Hb A from the transfused blood, but will still have increased amounts of Hb F and Hb A2 (table 1). Patients with combined heterozygosity for beta (0) and beta (+) thalassemia may produce small amounts of Hb A.

A more complete discussion of hemoglobin separation techniques is presented separately. (See "Laboratory diagnosis of the hemoglobinopathies".)

Diagnosis — The diagnosis of beta thalassemia major will have been made in all patients at around 6 to 12 months of age due to the presence of pallor, irritability, growth retardation, abdominal swelling due to hepatosplenomegaly, and jaundice. The laboratory examination at that time will show severe anemia with markedly abnormal hypochromic, microcytic red cells (picture 1) and with all of the classical findings of severe hemolytic anemia (eg, increased indirect bilirubin and lactate dehydrogenase and reduced or absent haptoglobin).

The diagnosis is confirmed on hemoglobin electrophoresis (table 1). Hemoglobin A is absent or severely reduced; only hemoglobins F and A2 are present. Variable amounts of hemoglobin A will be present in those who are subsequently treated with red cell transfusions, but levels of hemoglobins F and A2 will remain elevated.

CLINICAL HETEROGENEITY OF BETA THALASSEMIA

Overview — The beta thalassemia syndromes are remarkable for their heterogeneity, particularly in terms of clinical severity (table 2) [2,3]. Some of the factors contributing to this variability have been identified on the basis of differences in the mutations producing the beta thalassemic lesion (eg, beta (+) or beta (0) mutations that produce some or no beta globin, respectively), as well as interactions that modify the alpha-globin inclusion burden (eg, an accompanying alpha thalassemia).

- The genetic basis for the variability in clinical severity of homozygous beta (0) thalassemia was studied in a cohort of 316 Sardinian patients [81]. Clinical severity was assessed via the age at first transfusion. Phenotypic severity (ie, earlier age at the time of first transfusion) was explained to a large extent by genetic variants affecting fetal hemoglobin production (HBG2:g.-158C>T, BCL11A, HBS1L-MYB), with the remainder due to alpha globin gene defects and gender. (See "Clinical variability in sickle cell anemia", section on 'Fetal hemoglobin'.)

- Patients "homozygous" for beta thalassemia mutations (that is, inheriting a beta thalassemia mutation on each chromosome, even if they are not identical) usually exhibit some degree of alpha globin inclusion body formation, with consequent anemia, hemolysis, and varying degrees of ineffective erythropoiesis. The amount of alpha globin inclusion body formation and the degree of ineffective erythropoiesis correlate best with overall severity. The terms "beta thalassemia minor" and "beta thalassemia intermedia," attempt to reflect the fact that individuals carrying beta thalassemia mutations exhibit considerable clinical heterogeneity, requiring differences in approach to management. (See "Pathophysiology of beta thalassemia".)

- The vast majority of heterozygotes for beta thalassemia (eg, beta thalassemia trait) are asymptomatic [2]. This is thought to reflect the ability of the erythrocyte to catabolize some of the excess unpaired alpha-globin chains effectively; the burden is less because the patient is capable of producing approximately half the normal amount of beta globin.

Beta thalassemia minor — The terms beta thalassemia minor, beta thalassemia trait, and silent carrier of beta thalassemia are used to describe heterozygotes who carry one normal beta globin allele and one beta globin thalassemic allele. The vast majority of these patients are entirely asymptomatic, but do present an abnormal blood picture that is sometimes erroneously diagnosed as iron deficiency anemia.

Although the splenic volume, as assessed by ultrasonography, is 29 to 67 percent greater in those with thalassemia minor than in comparable controls [82,83], the spleen is palpable in less than 20 percent of subjects [82,84].

Typically, the blood count and peripheral blood film exhibit features similar to those seen in iron deficiency anemia (eg, hypochromia and microcytosis) (picture 2). However, as a rule, the microcytosis is much more profound, and the anemia much milder, than that seen in iron deficiency anemia. Patients with beta thalassemia minor/trait also tend to have total red blood cell counts higher than normal, often into the "polycythemic" range.

Patients with beta thalassemia trait almost always have a hematocrit >30 percent, and a mean corpuscular volume of the red cells (MCV) <75 fL. In contrast, patients with iron deficiency rarely become microcytic (MCV <80 fL) until the hematocrit has dropped below 30. Another potentially useful indicator is the red cell distribution width (RDW). The RDW in patients with thalassemia trait tends to be normal, since virtually all cells are hypochromic and microcytic. In contrast, there is considerable heterogeneity in cell size in the early and intermediate stages of iron deficiency, producing an increased RDW. (See "Mean corpuscular volume".)

The peripheral blood smear often reveals a large number of target cells, more dramatic than is seen in all but the most profound cases of iron deficiency, as well as teardrop-shaped red cells (dacrocytes), which are not seen in iron deficiency. Red blood cell survival is either normal or only slightly shortened; reticulocyte counts are normal or only slightly increased, and overt hemolysis is generally not present.

During pregnancy, women with beta thalassemia trait sometimes exhibit a tendency to develop a more profound "physiologic" anemia of pregnancy than normal mothers, and may require transfusion. However, pregnancy outcomes are generally favorable [85].

Some rare forms of heterozygous beta thalassemia are due to mutations that alter the structure of the beta globin chain near its carboxy terminus, producing elongated or truncated beta globin chains. Even though their initial rate of synthesis is normal, these mutant chains combine abnormally with alpha globin to produce highly insoluble hemoglobin dimers or tetramers. The precipitates generate severe inclusion body formation and a phenotype more

like severe beta thalassemia. These rare patients require management like patients with beta thalassemia major or intermedia. (See "Molecular pathology of the thalassemic syndromes", section on 'Dominant thalassemia trait due to nonsense codons in the final exon'.)

Protection against arterial thromboembolic events — A number of studies and a meta-analysis have indicated that beta thalassemia trait has a protective effect against arterial cardiovascular and cerebrovascular disease in male subjects [86,87]. This beneficial effect has been attributed to low serum cholesterol levels, slight anemia, and microcytosis, with a concomitant decrease in blood viscosity [88,89]. These intriguing hypotheses require further prospective follow-up studies.

Hemoglobin electrophoresis — On electrophoresis or high performance liquid chromatography (HPLC) in patients with beta thalassemia trait, over 90 percent of the hemoglobin will be hemoglobin A along with an elevation in the hemoglobin A2 value, sometime as high as 7 or 8 percent, and an increase in Hb F in about 50 percent of patients (table 1 and table 3).

As an example, in a study of 444 Chinese individuals with beta thalassemia trait, hemoglobin A2 levels, when measured by HPLC, were in the range of 5.6 ± 0.5 percent [90]. While mean hemoglobin A2 levels were slightly lower in those with both beta thalassemia trait and iron deficiency anemia (5.3 percent), all subjects with both conditions had hemoglobin A2 levels ≥3.5 percent. While others have agreed that the presence of iron deficiency does not compromise the diagnosis of high hemoglobin A2 beta thalassemia trait [91], this has not been a universal conclusion [92].

However, some forms of beta thalassemia trait are not associated with an elevated hemoglobin A2 level, such as those with delta-beta or gamma-delta-beta thalassemia trait or when beta thalassemia trait is co-inherited with a delta globin gene mutation [90,93,94]. Therefore, a normal concentration of hemoglobin A2 does not rule out the presence of beta thalassemia trait. (See "Structure and function of normal human hemoglobins", section on 'Hemoglobin A2'.)

More complex hemoglobin electrophoretic patterns may be seen in patients with beta thalassemia trait who have co-inherited a gene for sickle cell anemia (eg, sickle cell/thalassemia) (table 3 and table 4). These combinations are discussed in detail separately. (See "Variant sickle cell syndromes" and 'Effect of concomitant alpha thalassemia' below.)

Beta thalassemia intermedia

Overview — The term "beta thalassemia intermedia" (TI) refers to patients with symptomatic beta thalassemia who do not require transfusion during at least the first few years of life, and are able to survive into the second decade of life without chronic hypertransfusion therapy (eg, non-transfusion-dependent thalassemia) [95].

The term "beta thalassemia intermedia" is losing favor because it fails to address the genetic or clinical mechanisms for the phenotype of intermediate clinical severity [3]. However, it remains useful to refer to a category of patients who present special challenges in management, especially when these individuals are divided into those who require or do not require frequent blood transfusions.

The understanding that alpha globin inclusion burden is the predominant driver of clinical severity in patients with beta thalassemia has provided a useful paradigm for understanding some of the factors that contribute to the extraordinary clinical variability of this disease (table 2) [96]. As an example, some beta thalassemia mutations entirely ablate beta globin synthesis (ie, the beta(0) variants), while others are compatible with the production of up to 35 or 40 percent of the normal output of beta globin (ie, the beta(+) variants). Clearly, compound heterozygosity for a "severe" and a "mild" mutation, in terms of the degree to which beta-globin production is impaired, should result in a somewhat milder syndrome than homozygosity for a mutation that permits no beta-globin synthesis whatsoever.

Complications — Subjects with TI, while they may not require transfusion therapy at all, or as often as those with thalassemia major, have increased absorption of dietary iron, and may ultimately develop signs, symptoms,

and complications of iron overload (eg, cardiac dysfunction, end-stage liver disease including hepatocellular carcinoma, endocrine dysfunction) [97-101]. They may also suffer from the complications of chronic hypoxia, such as high cardiac output, increased pulmonary vascular resistance, pulmonary hypertension, and heart failure, and may also be prone to thrombotic complications. As a result, such patients should be monitored frequently for these complications. (See "Pathogenesis of pulmonary hypertension" and "Treatment of beta thalassemia", section on 'Beta thalassemia intermedia'.)

In one study of 584 patients with TI, older age and prior splenectomy were independently associated with an increased risk of most disease-related complications; splenectomy was protective only against the development of extramedullary hematopoiesis [101]. In this report, in which 70 percent of the subjects were over the age of 18 years, 56 percent had undergone splenectomy, and 76 percent were receiving either occasional or regular transfusions, complications included the following:

- Osteoporosis – 23 percent
- Extramedullary hematopoiesis – 21 percent
- Hypogonadism – 17 percent
- Cholelithiasis – 17 percent
- Thrombosis – 14 percent
- Pulmonary hypertension – 11 percent
- Abnormal liver function – 10 percent
- Leg ulcers – 8 percent [102]
- Hypothyroidism – 6 percent
- Heart failure – 4 percent
- Diabetes mellitus – 2 percent

Thus, while most patients with TI do not need regular blood transfusions in order to survive, the stigmata of the disease, including bone marrow expansion, hepatosplenomegaly, and chronic hemolytic anemia are present, even in milder forms of the disorder.

- At the milder end of the scale of TI, some of these patients will undergo normal puberty and survive into adult life. However, they may be subject to a number of complications with advancing age (eg, leg ulcers, thrombosis, extramedullary hematopoiesis, pulmonary hypertension, hypothyroidism, osteoporosis) [100].

- At the more severe end of the spectrum, children with TI develop a need for transfusions or splenectomy at earlier times, often at the onset of or during adolescence. This may reflect the increased demands of puberty and the prepubertal growth spurt on the production of red cells.

These patients present a therapeutic dilemma, namely, when to institute chronic transfusion therapy with its attendant complications [2]. Delay for the longest possible time is clearly desirable, given the life-long problems associated with transfusion therapy. On the other hand, excessive delay can lead to significant morbidity, similar to that seen in younger children with beta thalassemia major. It is important to realize, however, that progressive iron overload can develop in many of these children, even in the absence of chronic transfusion therapy, requiring consideration for the use of iron chelating agents.

Iron overload — As already noted, expansion of the erythroid marrow and accelerated erythroid turnover stimulate iron absorption from the gut, leading to excessive iron accumulation in the body in patients incapable of utilizing the excess iron to manufacture hemoglobin. When patients with non-transfusion-dependent thalassemia develop signs and symptoms of iron overload, they are similar in virtually all respects to those with beta thalassemia major. (See "Pathophysiology of beta thalassemia", section on 'Non-transferrin bound iron'.)

As an example, in a cross-sectional study of 168 subjects with TI and a mean age of 35 years, mean liver iron concentration, as determined by magnetic resonance imaging, was 8.4 ± 6.7 mg Fe/g dry weight (normal: <2; iron overload: >4) [103]. After adjusting for age, gender, splenectomy and transfusion status, and laboratory indices, a 1

mg Fe/g dry weight increase in liver iron concentration was independently and significantly associated with higher odds of thrombosis, pulmonary hypertension, hypothyroidism, osteoporosis, and hypogonadism.

The above results from a cross sectional study were confirmed in the ORIENT study, a retrospective longitudinal cohort study in 52 subjects with non-transfusion-dependent thalassemia, using data from five Middle East comprehensive care centers. Observations included the following [104]:

- Thirty-six subjects (69 percent) had at least one morbidity, while 17 (33 percent) had multiple morbidities. The most common morbidities were osteoporosis (48 percent), extramedullary hematopoiesis (19 percent), liver disease (17 percent), hypothyroidism (10 percent), hypogonadism (8 percent), and diabetes mellitus (8 percent).
- The cumulative incidence of at least one morbidity was zero, 53, and 100 percent for those with mean overall serum ferritins ≤300, 300 to <800, and ≥800 ng/mL, respectively. The cumulative incidence of multiple morbidities was 0, 5.9, and 59 percent for those with mean overall serum ferritins ≤300, 300 to <800, and ≥800 ng/mL, respectively.
- Kaplan-Meier survival curves for time-to-first morbidity indicated that morbidity-free survival at 10 years for subjects with an overall serum ferritin level ≤300 or ≥800 ng/mL were 100 and zero percent, respectively.

These results confirm the damaging effects of iron overload in this patient population, and support the use of a ferritin level ≥800 ng/mL to initiate iron chelation therapy in those with beta thalassemia intermedia. (See "Chelation therapy for thalassemia and other iron overload states", section on 'Iron chelation in transfusion-independent thalassemia'.)

Effect of concomitant alpha thalassemia — Alpha thalassemia is common in the same populations in which beta thalassemia is prevalent. Coinheritance of alpha thalassemia trait clearly ameliorates the severity of beta thalassemia, since the reduction in alpha globin synthesis (from the alpha thalassemia component) reduces the burden of alpha globin inclusions (from the beta thalassemia component) without greatly affecting the amount of actual hemoglobin made.

Effect of fetal hemoglobin levels — Fetal hemoglobin (HbF) synthesis persists to some degree in most patients with symptomatic beta thalassemia. In part, this reflects the tendency of "erythropoietic stress" to stimulate HbF production, even in adults. Elevated levels of HbF also appear to vary in the population via polymorphisms for heterocellular hereditary persistence of fetal hemoglobin, as well as mutations in the erythroid-enriched transcription factor KLF1. This important subject is discussed in depth separately. (See "Fetal hemoglobin (hemoglobin F) in health and disease", section on 'Acquired increases in HbF' and "Fetal hemoglobin (hemoglobin F) in health and disease", section on 'HbF in the thalassemias and hereditary persistence of fetal hemoglobin' and "Fetal hemoglobin (hemoglobin F) in health and disease", section on 'Kruppel-like factor 1 (KLF1)'.)

Persistent synthesis of HbF has two beneficial effects: it provides additional oxygen carrying capacity and the gamma globin chain binds some of the free alpha globin, thus reducing alpha globin inclusions. In some ethnic groups and locations thalassemia also tends to be milder, presumably because of increased HbF levels [105]. As an example, the effect of HbF levels on 10 measures of morbidity was assessed in 63 untransfused subjects with thalassemia intermedia who had never received HbF induction therapy [106]. The following observations were made:

- Levels of HbF correlated positively with total hemoglobin and negatively with non-transferrin bound iron.
- There was a strong negative correlation between the HbF level and the total number of morbidities (eg, extramedullary hematopoiesis, pulmonary hypertension, venous thromboembolism, heart failure, leg ulcers, abnormal liver function, endocrinopathy, osteoporosis).
- A HbF threshold of 63.7 percent had 95.5 and 100 percent sensitivity and specificity, respectively, for ensuring the absence of morbidity.

Other causes of disease variability — Although features of the globin genotype in families with thalassemia

account for some of the clinical variability encountered in this disorder, much remains to be explained. For example, siblings in some families appear to have identical globin genotypes, yet exhibit rather notable differences in clinical severity or in the prominence of individual manifestations of the disease. There is thus a substantial effort underway to use gene expression profiling, study of single nucleotide polymorphisms, and other technologies in an effort to associate polymorphic variations in other genes with altered clinical phenotype. To date, despite a considerable accumulation of preliminary data, no definitive leads are available. (See "Fetal hemoglobin (hemoglobin F) in health and disease", section on 'Hemoglobin switching: genetic basis of HbF expression' and "Clinical variability in sickle cell anemia".)

Diagnosis and differential diagnosis — The diagnosis of beta thalassemia minor or intermedia should be entertained in patients of any age with microcytic, hypochromic red cells (picture 3). As the beta thalassemias show considerable heterogeneity, patients may or may not have symptoms referable to anemia, may have variable degrees of splenomegaly and variable degrees of hemolysis.

The major differential diagnosis in patients with microcytic, hypochromic red cells includes iron deficiency and the anemia of (chronic) inflammation, as follows:

- **Iron deficiency** – Patients with iron deficiency will have low levels of serum iron and ferritin and increased levels of transferrin (total iron binding capacity). Those with iron deficiency rarely become microcytic (mean corpuscular volume (MCV) <80 fL) until the hematocrit has dropped below 30 percent. The red cell distribution width (RDW) is usually increased and the total red cell count is decreased in concert with the degree of anemia. A cause for blood loss will be obvious in most patients.

- **Anemia of inflammation** – Patients with the anemia of chronic inflammation will have low levels of serum iron and transferrin. Levels of ferritin will be normal or increased. An inflammatory, infectious, or malignant disease is usually the underlying cause.

- **Thalassemia** – Patients with thalassemia will have normal to increased levels of serum iron and ferritin. Levels of transferrin will be normal or decreased. Patients with beta thalassemia trait almost always have a hematocrit >30 percent, and a mean corpuscular volume (MCV) <75 fL. The RDW tends to be normal. The total red cell count is usually normal to increased in those with beta thalassemia trait, reflecting the presence of an increased number of smaller than normal red cells. At least one of the patient's parents will also be affected. A family history of "iron deficiency anemia not responding to treatment with iron" is common.

The diagnosis of a beta thalassemic condition is confirmed on hemoglobin electrophoresis (table 1 and table 3). Hemoglobin A will be the major hemoglobin present. Levels of hemoglobin A2 are increased in virtually all patients, while levels of hemoglobin F are increased in about 50 percent of patients. (See "Laboratory diagnosis of the hemoglobinopathies".)

If hemoglobin S is present on electrophoresis along with hypochromic, microcytic red cells, and iron deficiency is absent, one of the sickle cell/thalassemia conditions is present (table 3 and table 4). (See "Variant sickle cell syndromes".)

THE ALPHA THALASSEMIA SYNDROMES — Alpha thalassemia is due to impaired production of alpha globin chains, leading to a relative excess of beta globin chains. The toxicity of the excess beta globin chains on the red cell membrane skeleton appears to be less than that of the excess partially oxidized alpha globin chains in beta thalassemia. (See "Pathophysiology of alpha thalassemia", section on 'Definitions'.)

Nomenclature and diagnostic patterns — The normal subject has four functional alpha globin genes, two on each chromosome 16 (ie, aa/aa). There are four deletional alpha thalassemia syndromes, reflecting the loss of one, two, three, or all four of these alpha chain genes (table 1):

- **Alpha thalassemia minima** (silent carrier of alpha thalassemia, heterozygosity for alpha (+) thalassemia, heterozygosity for the alpha thalassemia-2 trait) is due to the loss of **one** of the four alpha globin genes (ie, aa/a-).

- **Alpha thalassemia minor** is due to the loss of **two** of the four alpha globin genes. This can come about in two different ways, as follows:
    - Heterozygosity for the alpha thalassemia-1 trait (heterozygosity for alpha (0) thalassemia), in which both alpha genes on one of the two chromosomes have been deleted (ie, cis deletional form, aa/--)
    - Homozygosity for the alpha thalassemia-2 trait (homozygosity for alpha (+) thalassemia), in which one of the alpha genes has been deleted on each of the two chromosomes (ie, trans deletional form, a-/a-)
- **The deletional form of hemoglobin H disease** is due to the loss of **three** of the four alpha globin loci, due to compound heterozygosity for both the alpha thalassemia-2 trait and the alpha thalassemia-1 trait (ie, a-/--).
- **The non-deletional form of hemoglobin H disease** is due to the loss of **two** of the four alpha globin loci along with an alpha chain mutation in one of the two remaining loci, due to compound heterozygosity for both the alpha thalassemia-1 trait and hemoglobin Constant Spring (ie, --/aa^{CS}).
- **Hydrops fetalis with Hb Barts** is due to loss of all **four** alpha globin loci secondary to homozygosity for the alpha thalassemia-1 trait (ie, --/--).

The majority of patients with alpha thalassemia, especially in Asia and Africa, have lost alpha globin gene function because of deletion of one, two, three, or all four structural alleles [107,108]. However, non-deletion alleles are also common, especially in the Mediterranean area, as are mutations producing highly unstable alpha globin variants that lead to failure to produce intact hemoglobin during erythropoiesis. (See "Pathophysiology of alpha thalassemia".)

A major clinical feature associated with inheritance of alpha thalassemia is the interaction of alpha thalassemia trait with beta globin hemoglobinopathies, including beta thalassemia and sickle cell anemia. (See 'Effect of concomitant alpha thalassemia' above and "Variant sickle cell syndromes", section on 'Sickle-alpha thalassemia'.)

Alpha thalassemia minima — Alpha thalassemia minima is essentially asymptomatic. Adult patients with alpha thalassemia minima are not anemic, their red cells are not microcytic, and their hemoglobin electrophoresis pattern is normal. The complete blood count and peripheral smear are usually normal, although very slight hypochromia and microcytosis might be evident by microscopic examination. Alpha thalassemia minima becomes apparent in families usually because individuals carrying this allele can, when mating with a partner carrying the alpha thalassemia-1 allele, give rise to an infant with HbH disease. The diagnosis of alpha thalassemia minima can be reliably made only via DNA analysis.

Alpha thalassemia minor — Alpha thalassemia minor resembles mild beta thalassemia trait. Adult patients with alpha thalassemia minor