REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

β-Thalassemias

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THE THALASSEMIAS ARE A GROUP OF RECESSIVELY INHERITED DISORDERS characterized by reduced or no production of hemoglobin and chronic anemia of varying severity.[1] The evolutionary association between the thalassemia carrier state and resistance to malaria explains its high prevalence in the area extending from sub-Saharan Africa, the Middle East, and the Mediterranean basin to Southeast Asia.[2] Population migrations have also introduced thalassemia to Europe and the Americas, where the disease was previously relatively rare.[3] Challenges to the implementation of prevention programs and improved newborn survival have translated to continued burden of incident disease in both resource-limited regions and multiethnic cities in developed countries. Advances in care have increased the life expectancy of adults with thalassemia, although the associated resource use is high.[3]

Thalassemia is subdivided into α-thalassemia and β-thalassemia, depending on the underlying genetic mutation and affected globin-chain subunits within the hemoglobin tetramer. The α-thalassemias have been reviewed previously in the *Journal*.[4] This review focuses on β-thalassemias.

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FROM BENCH TO BEDSIDE

HEMOGLOBIN SYNTHESIS

Several forms of hemoglobin are expressed during embryonic, fetal, and adult life, and combinations of these forms may be found at various times during human development. The hemoglobin tetramer is made of two α-globin chains or α-like (ζ)–globin chains and two β-globin chains or β-like (ε, γ, δ)–globin chains, encoded by multigene clusters on chromosomes 16 and 11, respectively. Gene expression and switching on these clusters parallel human development at different sites of erythropoiesis. During early gestation, embryonic hemoglobins ($\zeta_2\varepsilon_2$, $\alpha_2\varepsilon_2$, $\zeta_2\gamma_2$) predominate in erythroid cells in the yolk sac. For the remainder of fetal life, fetal hemoglobin (HbF [$\alpha_2\gamma_2$]) is the main component of red cells produced initially by the spleen and liver and later by the bone marrow. The key switch from γ-globin to β-globin gene expression begins around week 12 of gestation and is completed by 6 months of age, after which the majority (>95%) of hemoglobin in red cells is adult hemoglobin (HbA [$\alpha_2\beta_2$]), with minor concentrations of HbA_2 ($\alpha_2\delta_2$) and HbF.[2]

MOLECULAR PATHOGENESIS

β-Thalassemia is caused by mutations resulting in a single nucleotide substitution, small deletions or insertions within the β-globin gene or its immediate flanking sequence, or in rare cases, gross deletions. These mutations result in reduced production of β-globin chains and HbA. More than 350 β-thalassemia mutations have been described, and they are commonly assigned a severity index, with β^+ denoting mild mutations that cause a relative reduction of β-globin chain synthesis and β^0 referring to severe mutations that can lead to a complete absence of β-globin chain product.

The severity of anemia, need for transfusions, and clinical morbidity in

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β-thalassemia are closely tied to the degree of imbalance between α-globin and β-globin chains. Deficient production of β-globin chains leads to the accumulation of excess, unstable α-globin tetramers in erythroid cells. Free α-globin protein is unstable and generates cytotoxic reactive oxidant species and cellular precipitates that impair the maturation and viability of red-cell precursors, resulting in ineffective erythropoiesis and premature hemolysis of circulating red cells.[2,5] Thus, patients who have severe β-thalassemia mutations in the homozygous or compound heterozygous state tend to have more severe clinical manifestations, whereas patients who coinherit α-thalassemia tend to have a milder disease. In heterozygous patients, who are usually asymptomatic, overt disease may develop with coinheritance of extra α-globin genes (duplications) as a result of the increased amount of free α-globin protein.[6] In addition, red-cell precursors in β-thalassemia can detoxify and tolerate a modest pool of free α-globin, which is stabilized by the molecular chaperone α-hemoglobin–stabilizing protein (AHSP) and eliminated by the ubiquitin–proteasome system and autophagy.[5,7] Altered levels of AHSP expression influence the severity of β-thalassemia,[8] and loss of the gene encoding autophagy-activating Unc-51–like kinase 1 (*Ulk1*) can reduce autophagic clearance of α-globin in red-cell precursors and increase disease severity.[9]

The degree of imbalance between α-globin and β-globin chains can also be reduced by the more effective synthesis of γ-globin chains and HbF after birth. Several genes are involved in modifying the γ-globin chain response; some are encoded in the β-globin gene cluster, and others are on different chromosomes. Genomewide association studies examining common variation in HbF levels have identified BCL11A (a multi-zinc-finger transcriptional regulator) as a key regulator of the switch from fetal to adult hemoglobin and HbF silencing.[10,11] BCL11A represses the genes encoding HbF and is believed to be regulated at the level of messenger RNA translation through the RNA-binding protein LIN28B.[12,13] Genetic variation in the expression of BCL11A and persistent HbF production have been shown to reduce the clinical severity of β-thalassemia.[14,15]

GENOTYPE–PHENOTYPE ASSOCIATION

The three main β-thalassemia phenotypes are conventionally assigned on the basis of the clinical presentation, with the recognition that certain genetic profiles are commonly, but not exclusively, associated with specific phenotypes (Fig. 1). β-Thalassemia trait, or β-thalassemia minor, which results from heterozygous inheritance of a β-thalassemia mutation, is characterized by borderline asymptomatic anemia with microcytosis and hypochromia.[16] A recent study showed higher hospitalization rates and morbidity among patients with this β-thalassemia phenotype than among healthy controls, but the reasons remain to be explored.[17] Patients may inherit a completely silent β-thalassemia mutation that is not associated with any hematologic abnormalities (β-thalassemia silent carriers).[18] If both parents are carriers of a thalassemia mutation, then genetic counseling about the risk of having children with β-thalassemia is indicated.

Patients who are homozygous or compound heterozygous for β-thalassemia mutations can have β-thalassemia major or intermedia.[16] Patients with β-thalassemia major generally present early in life, with severe anemia and symptoms, whereas patients with β-thalassemia intermedia tend to present later in life, with mild-to-moderate anemia and symptoms.[2,16] The severity of β-thalassemia mutations, status with respect to coinheritance of α-thalassemia, and genetic capacity for continued or increased HbF production are some of the factors that can determine whether β-thalassemia is manifested as the intermedia or major phenotype. β-Thalassemia intermedia may also result from a heterozygous state associated with increased production of α-globin chains by a triplicated or quadruplicated α-globin genotype, from dominant (inclusion-body) β-thalassemia, or from deletion forms of δβ-thalassemia (involving deletion of δ- and β-globin genes) and hereditary persistence of fetal hemoglobin (HPFH).[2,16,19]

Hemoglobin E (HbE) is an abnormal hemo-

Figure 1 (facing page). Genotypes, Phenotypes, and Transfusion Requirements in Patients with β-Thalassemia.

Additional modifiers of phenotype severity may include environmental factors such as coinfection with malaria or polymorphisms that ameliorate the severity of specific complications.[16] β-Thalassemia intermedia may be associated with deletion forms of δβ-thalassemia and hereditary persistence of fetal hemoglobin (HbF) or dominant (inclusion-body) β-thalassemia.[16] Clinical manifestations of β-thalassemia intermedia and β-thalassemia major at presentation, in addition to anemia, may include jaundice, growth retardation, splenomegaly, and facial and bone deformities. HbE denotes hemoglobin E.

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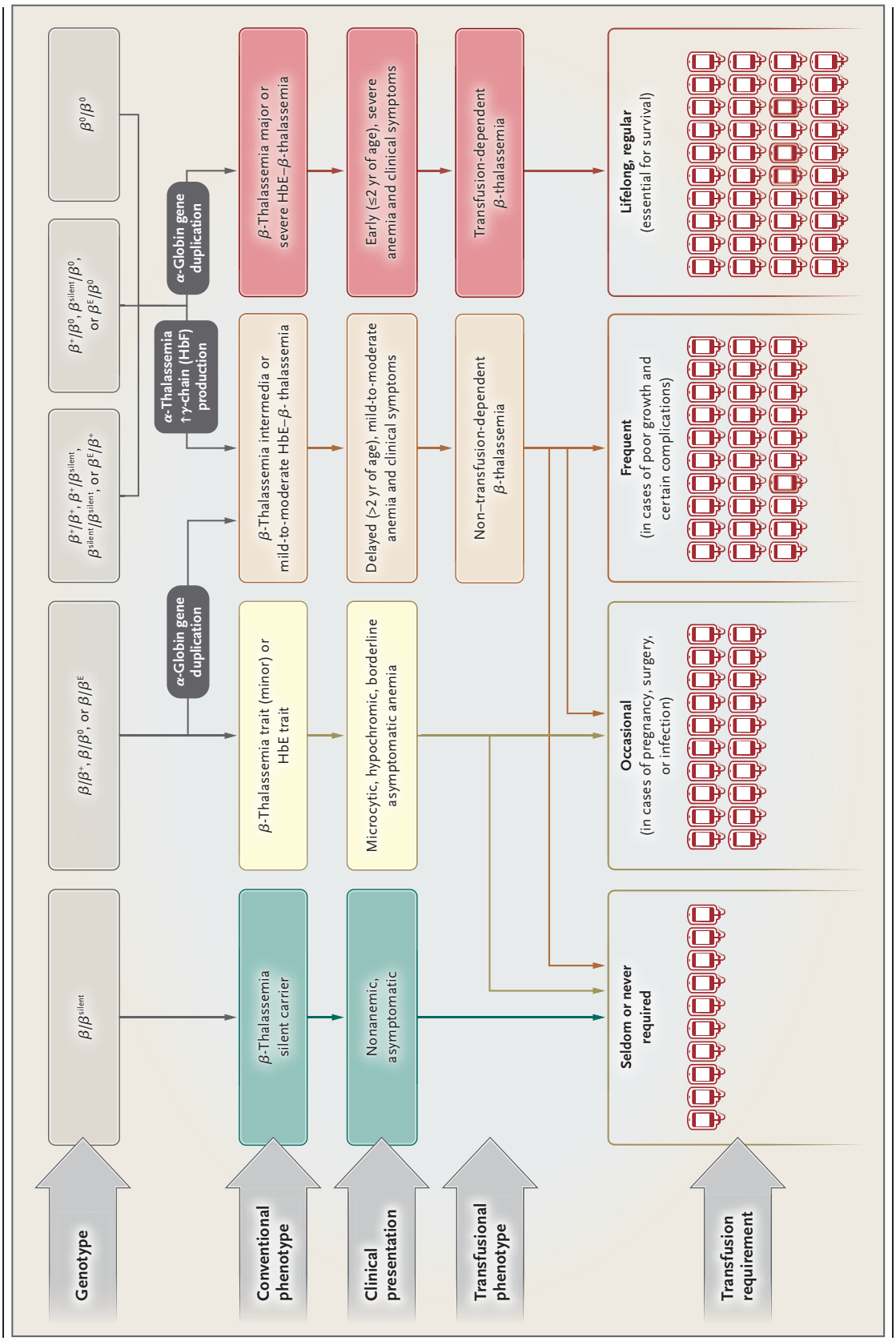

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globin that results from a single point mutation in the β-globin gene and behaves like a β^+ mutation. When this mutation is coinherited with a β-thalassemia mutation, patients are classified as having HbE–β-thalassemia, which can vary in severity from mild or moderate (like β-thalassemia intermedia) to severe (like β-thalassemia major).[20] Disease severity is also governed by the genetic modifiers mentioned above.[16,20] The remarkable ability of children with HbE–β-thalassemia to adapt to low hemoglobin levels, which has been attributed to an erythropoietin response that is stronger in early life than in later life, may delay or reduce the need for transfusion.[21]

PHENOTYPES REVISITED

In the past decade, a new phenotype classification has started to replace the aforementioned conventional phenotypes, aiming to highlight the transfusion requirement for the individual patient throughout the disease course, since this requirement has major effects on associated pathophysiological features and practical management. Patients with transfusion-dependent β-thalassemia (β-thalassemia major or severe HbE–β-thalassemia) require lifelong, regular transfusions for survival, whereas patients with non–transfusion-dependent β-thalassemia (β-thalassemia intermedia or mild-to-moderate HbE–β-thalassemia) require no transfusions, occasional transfusions because of specific circumstances (e.g., pregnancy, surgery, or acute infection), or frequent transfusions but for a limited period (e.g., to support a growth spurt during childhood or manage a clinical complication) (Fig. 1).[16,22,23] The non–transfusion-dependent and transfusion-dependent classifications for patients with β-thalassemia are now commonly used for clinical trial eligibility and international management guidelines.

CONFIRMING THE DIAGNOSIS

If β-thalassemia is suspected on the basis of the physical examination, personal and family history, and red-cell indexes (low mean corpuscular volume, low mean corpuscular hemoglobin level, and normal red-cell distribution width), the diagnosis can be confirmed by means of hemoglobin electrophoresis or high-performance liquid chromatography. DNA analysis may be required to confirm the diagnosis of HbE and identify the specific β-thalassemia genotype.[22,23]

Figure 2 (facing page). Pathophysiological and Clinical Manifestations of β-Thalassemia.

The circled numbers and letters link complications with causal risk factors.

EPIDEMIOLOGY AND GLOBAL DISTRIBUTION

Data on the epidemiology of β-thalassemia are limited. According to data that are more than 10 years old, β-thalassemia carriers account for approximately 1.5% of the world population, and around 40,000 affected infants are born each year, with half of them classified as transfusion-dependent.[24] More than 90% of patients with β-thalassemia live in a geographic "belt" extending from Africa to Southern Europe and the Middle East, toward Southeast Asia, where HbE–β-thalassemia is most common.[2] Individual data from certain geographic regions and collaborative registries have been reviewed recently.[3] In some countries, such as Cyprus, Greece, and Italy, successful screening (premarital and prenatal) and prevention programs have reduced the number of affected persons. In other regions, such programs have often been hampered by limitations in local public health agendas or cultural and religious beliefs that restrict implementation.[3]

Increases in the number of patients and in the use of health services in Europe and North America are becoming more evident.[25,26] These increases reflect not only the gradual introduction of carriers through historical population migrations but also more recent movements of refugees from areas of conflict, as well as increased rates of adoption of children.[3,27,28] Altogether, the global burden of thalassemia is increasing, since many of these immigrants are not covered by screening programs, and affected patients do not always have adequate access to care.

CLINICAL IMPLICATIONS

To understand complications associated with β-thalassemia, it is imperative not only to be familiar with the underlying pathophysiology but also to consider how the pathophysiology is influenced by conventional therapies such as splenectomy, transfusions, and iron chelation (Fig. 2). These therapies become embedded in the patient's clinical profile, and their use, or lack thereof, determines which complications are likely to be observed throughout the disease course.

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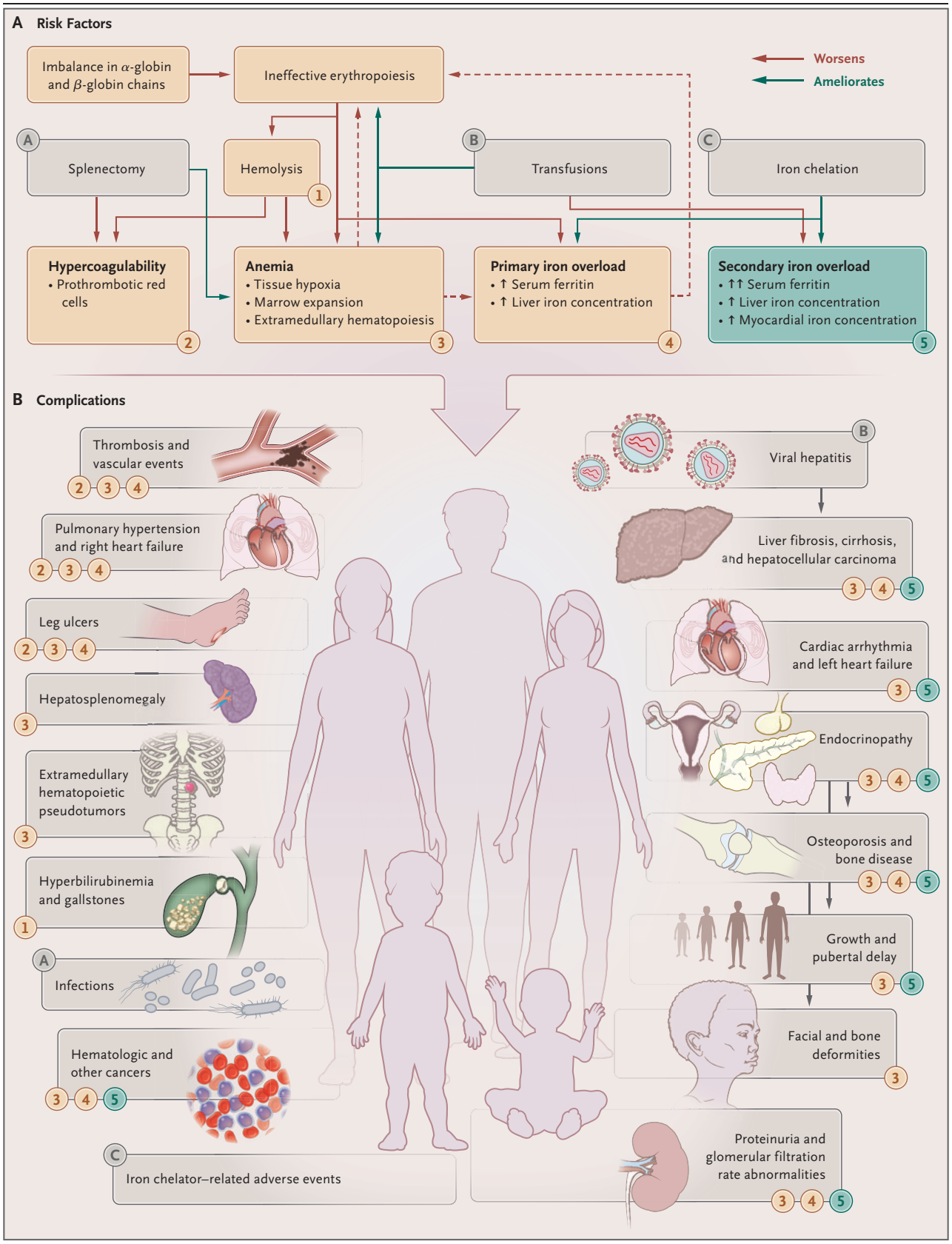

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Ineffective erythropoiesis and peripheral hemolysis lead to a state of chronic anemia that can cause growth and developmental delay, typical anemia-related symptoms such as fatigue, and leg ulcers and can promote organ failure in adolescents and young adults.[1,29] An independent effect of anemia on psychological well-being has also been reported.[30]

Ineffective erythropoiesis leads to marrow expansion and associated bone changes, pain, and deformity, which account for characteristic features of β-thalassemia such as craniofacial protrusions. Compensatory extramedullary foci that can undergo hematopoiesis also become activated, including the spleen and liver (hepatosplenomegaly) and other tissues in the body, where they can grow into extramedullary hematopoietic pseudotumors; if they emerge in areas such as the paraspinal canal or chest, these pseudotumors can cause serious compression and may require emergency management.[1,29]

Peripheral hemolysis in β-thalassemia causes red cells to express prothrombotic markers on their surface, leading to a hypercoagulable state, which is further promoted by platelet activation, microparticles, and other coagulation anomalies.[31] Clinically, these disorders can be manifested as venous and arterial thrombosis, pulmonary hypertension, and cerebrovascular events, including silent infarcts, which increase with aging.[32-34]

Although estimates of the incidence and prevalence of these complications stem from small, single-center studies, it is evident that they are more commonly encountered in patients with non–transfusion-dependent β-thalassemia than in patients with transfusion-dependent β-thalassemia (or those with non–transfusion-dependent β-thalassemia who are receiving transfusions), since transfusion therapy can ameliorate the anemia and ineffective erythropoiesis.[23,33] These complications may still be observed, however, with delayed or suboptimal transfusions in patients with transfusion-dependent β-thalassemia, especially those with severe anemia. In a study involving patients with non–transfusion-dependent β-thalassemia, the severity of anemia (each decrease of 1 g per deciliter in the hemoglobin level) was correlated with the risk of complications when the hemoglobin level was less than 10 g per deciliter; at higher levels, which were found in one third of the patients, no complications were identified.[35] Although splenectomy may raise hemoglobin levels, it reverses the scavenging role of the spleen in ridding the body of pathologic red cells, which is why morbidity, especially vascular disease, is increased among patients who have undergone splenectomy.[32,33]

Iron overload remains one of the most relevant clinical considerations in β-thalassemia. The iron burden has classically been measured through analysis of serum ferritin levels, but developments in magnetic resonance imaging (MRI) have allowed quantification of the iron concentration in target organs in order to tailor management. MRI techniques are currently used to measure the myocardial iron concentration (by T2*-weighted MRI) and the liver iron concentration (by T2- or T2*-weighted MRI; T2 and T2* denote relaxation time); liver iron concentration is also a surrogate for the total-body iron level.[36] The difference between T2-weighted and T2*-weighted images depends on how the scanner formed the echo. T2* is measured for gradient-formed echoes, whereas T2 is measured if radiofrequency pulses are used to form the echo (spin echo). T2 and T2* are reported in milliseconds (or through their reciprocals, R2 and R2*, in Hertz) and can be converted to milligrams of iron per gram of dry weight using calibration curves validated against iron concentrations measured in biopsy specimens. The techniques are internationally reproducible but require special expertise and calibration for appropriate application and interpretation.[37-39]

In patients with transfusion-dependent β-thalassemia, transfusional iron intake saturates the capacity of serum transferrin and leads to the emergence of non–transferrin-bound iron species that can readily accumulate in body tissues (commonly the liver, followed by the heart and endocrine organs), causing damage to vital organs.[40] Repeated measurements showing serum ferritin levels above 2500 ng per milliliter are associated with an increased risk of heart disease and death,[41] whereas levels below 1000 ng per milliliter are associated with prolonged survival.[42] Liver iron concentrations above 7 mg per gram are associated with an increased risk of liver disease, and concentrations above 15 mg per gram are associated with an increased risk of heart disease.[22] T2*-weighted MRI measurements of myocardial iron of less than 20 msec are associated with cardiac arrhythmia and those

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of less than 10 msec are associated with heart failure or death.[43,44] The risk of death due to cardiac iron overload in patients with transfusion-dependent β-thalassemia has decreased since the introduction of iron chelation in 1967 and was further reduced with the introduction of oral chelators and advanced imaging in the early 2000s. For example, in Cyprus, survival to the age of 30 years increased by 8% in the period from 2000 to 2018, as compared with the period from 1980 to 1999. Similar trends have also been reported in registries from the United Kingdom and Greece. In contrast, low survival rates continue to be reported in some resource-limited countries, especially for patients who have received inadequate blood transfusion and iron-chelation therapy, with less than half of patients reaching their fourth decade of life.[3]

Although it has traditionally been assumed that, for patients with non–transfusion-dependent β-thalassemia, iron overload does not develop in the absence of transfusions, a bidirectional relationship between ineffective erythropoiesis and primary iron overload has been revealed in such patients.[45] Ineffective erythropoiesis and hypoxia lead to decreased production of the hepatic hormone hepcidin, which in turn results in increased intestinal iron absorption and its release from macrophages in the reticuloendothelial system. Erythroferrone, a hormone secreted by erythroblasts as a consequence of activation of the erythropoietin receptor–Janus kinase 2–signal transducer and activator of transcription 5 (EPOR–JAK2–STAT5) pathway, is the main erythroid regulator of this process, making it an interesting target for drug development. Another factor involved in hypoxia-induced hepcidin suppression is platelet-derived growth factor BB (PDGF-BB). Growth differentiation factor 15 (GDF15) and twisted gastrulation 1 (TWSG1) have also been proposed as potential erythroid regulators of hepcidin, but their roles were subsequently challenged.[45] The final result of hepcidin suppression — slow but continued accumulation of iron, with preferential storage in the liver (and a notable absence of iron storage in the heart) — has been confirmed by studies showing clinically significant liver iron concentrations in patients with non–transfusion-dependent β-thalassemia, although with lower serum ferritin levels than those in patients with transfusion-dependent β-thalassemia and the same liver iron concentration. Observational studies have confirmed an association between iron overload (liver iron concentration >5 mg per gram and serum ferritin level >800 ng per milliliter) and several complications in patients with non–transfusion-dependent β-thalassemia, including hepatic fibrosis and cancer, proteinuria and renal failure, and endocrine and bone disease.[23,46] Vascular disease can also result from iron-induced endothelial damage, which further promotes hypercoagulability.[23,46]

Advancing age remains one of the most important risk factors for complications associated with β-thalassemia.[47,48] Many of the aforementioned clinical complications, such as vascular and hepatic disease, develop over a period of years. In addition to hepatic cancer, hematologic and other solid cancers have been reported in older patients with β-thalassemia and have been attributed to chronic stress in the bone marrow and iron overload.[48] In addition, with improved survival among such patients, other complications can develop, such as heart disease, diabetes, renal disease, and cancers associated with risk factors in the non-thalassemia population. Advancing age also uncovers several social and psychological challenges related to marriage, work, and social integration.[48] Furthermore, the quality of life can be substantially impaired in patients with β-thalassemia because of the burden of disease and the need for long-term treatment, and psychiatric disorders that increase the need for health care are not uncommon.[49]

MANAGEMENT

Available options for the management of β-thalassemia are summarized in Figure 3, and approaches to monitoring and management for specific complications are listed in Table 1.[22,23,29,48] International and local management guidelines for β-thalassemia are widely available but are based primarily on expert opinion; few recommendations are driven by results from randomized clinical trials. In addition to the treatment options discussed below, all patients should receive appropriate vitamins and other supplements necessary for well-being and support of hematopoiesis and should be considered for psychosocial support. Management considerations in special situations, including pregnancy, have been reviewed elsewhere.[22,23,48,50]

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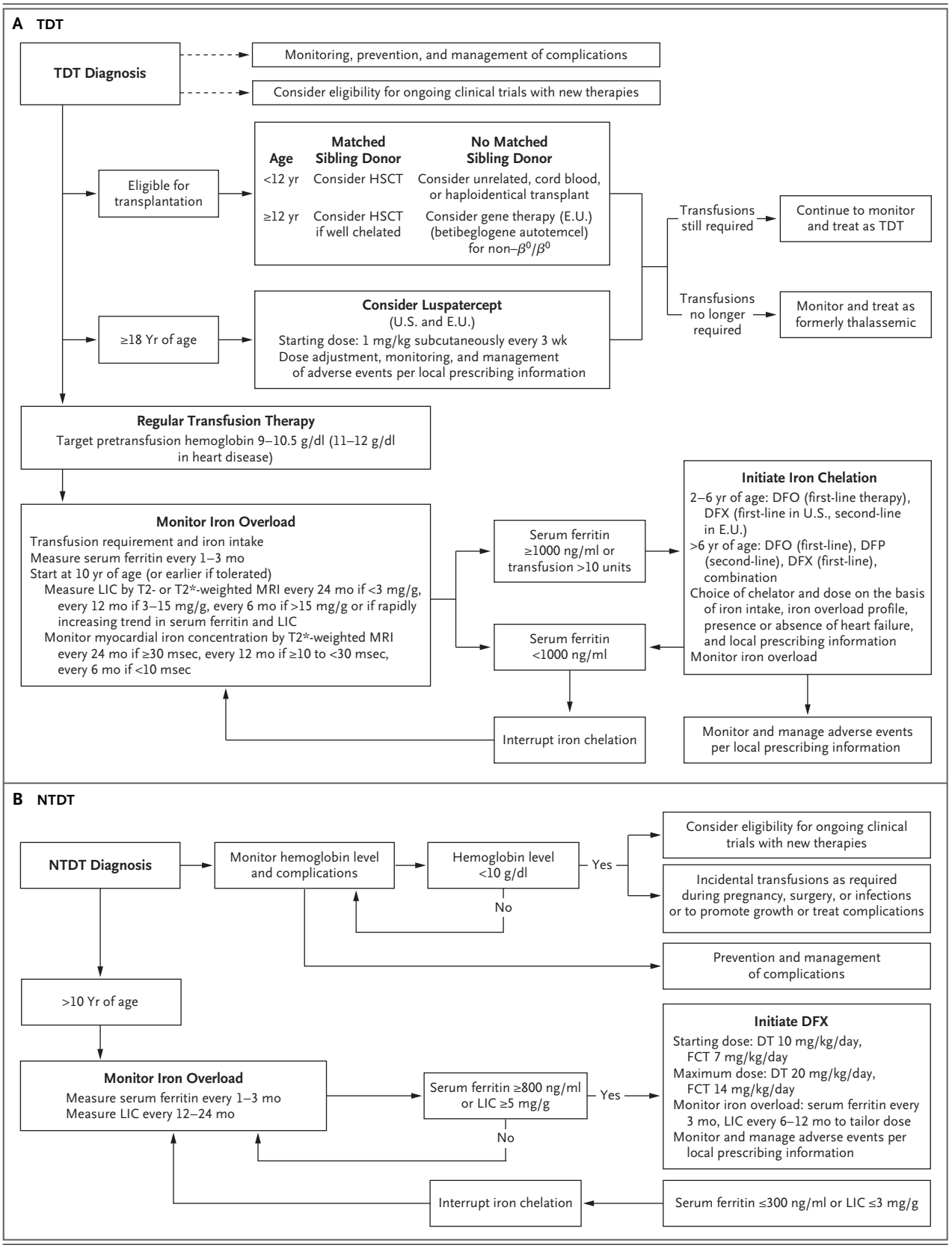

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Figure 3 (facing page). Treatment Options for β-Thalassemia.

Panel A shows the treatment options for patients with transfusion-dependent β-thalassemia (TDT). T2-weighted (spin-echo) MRI is used to measure liver iron concentration (LIC), whereas T2*-weighted (gradient-echo) MRI can be used to measure both LIC and myocardial iron concentration; measurements are reported in milliseconds and can be converted to milligrams of iron per gram of dry weight. Panel B shows the options for patients with non–transfusion-dependent β-thalassemia (NTDT). In addition to the treatment options shown, splenectomy may be considered in patients who require but are unable to receive transfusion and iron-chelation therapy or in those with clinically symptomatic splenomegaly or hypersplenism. Splenectomy is becoming more and more obsolete, owing to the increased risk of infections and the rate of complications in general and vascular disease in particular. Data from small, nonrandomized clinical trials have shown improvements in anemia and a reduced transfusion requirement with the use of hydroxyurea, although the effects were often modest or not durable. Few observational studies have shown that patients with NTDT who were receiving hydroxyurea had lower rates of complications such as leg ulcers, extramedullary hematopoietic pseudotumors, pulmonary hypertension, and endocrinopathy. These observations were mostly noted in subgroups of patients with a specific polymorphism (e.g., *XmnI*).[23] In patients with TDT, the dose (subcutaneous) of deferoxamine (DFO) is 30 to 60 mg per kilogram of body weight per day, given over a period of 8 to 12 hours for 5 to 7 days per week. Common adverse events include ocular and auditory symptoms, bone-growth retardation, local reactions, and allergy. The deferiprone (DFP) dose (given orally three times a day) is 75 to 100 mg per kilogram per day. Common adverse events include gastrointestinal symptoms, arthralgia, agranulocytosis, and neutropenia. The deferasirox (DFX) dose (given orally once a day) is 20 to 40 mg per kilogram per day (dispersible tablet [DT]) or 14 to 28 mg per kilogram per day (film-coated tablet [FCT]). Common adverse events include gastrointestinal symptoms, increased creatinine levels, and increased hepatic enzyme levels. In patients with NTDT, if the serum ferritin level is more than 300 but less than 800 ng per milliliter and the LIC measurement is not possible, chelation may still be considered when other clinical or laboratory measures are indicative of iron overload (IOL).[22] In studies involving patients with NTDT, DFX (DT) at doses of up to 30 mg per kilogram per day were used, without additional safety concerns.[23] E.U. denotes European Union, and U.S. United States.

TRANSFUSION AND IRON CHELATION

Regular transfusions are administered in transfusion-dependent patients to achieve target pretransfusion hemoglobin levels of 9 to 10.5 g per deciliter (11 to 12 g per deciliter in patients with heart disease). Although there are regional variations in transfusion practices,[51] advances in donor blood screening and preparation have decreased the rates of alloimmunization and bloodborne infections in most countries.[22]

Transfusion-dependent patients should be monitored for iron overload with the use of serum ferritin measurements and hepatic and myocardial MRI, and iron chelation should be administered shortly after transfusion of 10 packed red-cell units or when the serum ferritin level is 1000 ng per milliliter or higher. Three iron chelators, used alone or in combination, are currently available for managing iron overload: subcutaneous deferoxamine and the oral agents deferiprone and deferasirox (dispersible and film-coated tablets). Deferoxamine and deferasirox are approved for treatment in patients older than 2 years of age, whereas deferiprone is approved as second-line therapy in patients older than 6 years of age,[22] although a recent randomized trial showed its efficacy and safety in younger patients.[52] Ample data for all three chelators show their ability to reduce systemic, hepatic, and myocardial iron overload as monotherapy or combination therapy (deferoxamine and deferiprone), with limited head-to-head comparisons between oral chelators.[53-58] The magnitude of the reduction in iron overload varies according to the organ and the agent, and high doses may be required to reverse cardiac siderosis. Oral chelators have an established advantage over deferoxamine with respect to adherence to the treatment regimen, and the new film-coated deferasirox tablet is associated with improved patient-reported outcomes, as compared with the dispersible form.[22,59] Otherwise, the choice of iron chelator should be based on local guidelines, clinical judgment, and the individual patient's iron overload profile. Successful treatment depends on dose adjustment according to ongoing iron intake, monitoring, attention to adherence issues, and management of adverse events. Continuous parenteral deferoxamine remains the first choice for patients who already have cardiac dysfunction, and data on the benefit of deferoxamine combined with deferiprone are also available.[22]

Patients with non–transfusion-dependent β-thalassemia and a hemoglobin level of less than 10 g per deciliter are at increased risk for complications.[35] Owing to the risk of secondary iron overload, it is not advisable to recommend

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Table 1. Monitoring for and Management or Prevention of Specific Complications in Patients with β-Thalassemia.*

Complication	Monitoring†	Management or Prevention‡
Thrombosis and vascular events	Thrombotic risk assessment during inpatient admissions, pregnancy, or surgery, especially in adults, patients with NTDT, splenectomized patients, those with a history of thrombosis, and those with a platelet count ≥500×10^9/liter or Hb <10 g/dl	Preventive anticoagulant therapy per local standards, based on thrombotic risk Aspirin in splenectomized patients with platelet count ≥500×10^9/liter Lower prevalence of primary and secondary vascular events in patients with NTDT receiving transfusions
Pulmonary hypertension	Echocardiographic assessment of TRV, especially in adults, patients with NTDT, splenectomized patients, and those with history of thrombosis, platelet count ≥500×10^9/liter, or Hb <10 g/dl — assessment every 3–5 yr if TRV <2.5 m/sec or every 12 mo if TRV ≥2.5 m/sec; RHC if TRV >3.2 m/sec or if TRV 2.5–3.2 m/sec with symptoms	Potential preventive role for anticoagulant therapy in at-risk patients Treatment guided by evaluation to confirm the form of pulmonary hypertension Lower prevalence among patients with NTDT receiving HU, transfusions, or ICT
Cardiac arrhythmia and heart failure	Echocardiography and ECG (age >10 yr) — every 12 mo if LVEF ≥56% or every 3–6 mo if LVEF <56% or if there are symptoms	Evidence of reversal of cardiac dysfunction in patients with TDT receiving continuous parenteral DFO or a combination of DFO and DFP
Viral hepatitis	Serologic testing for HCV and HBV in regularly transfused patients — every 12 mo	Blood product screening, vaccination for HBV at start of transfusion, vaccination for HAV Treatment per local standards DAA (preferred) or peginterferon plus ribavirin for HCV
Liver fibrosis, cirrhosis, and HCC	ALT, AST, bilirubin measurements — every 3 mo or every 1 mo if >5 ULN Liver ultrasound (age ≥18 yr) — every 12 mo, or every 6 mo if values are abnormal Transient elastography for hepatic stiffness, if available (in adults) — every 12–24 mo	Adequate management of viral hepatitis, when present Treatment per local standards Evidence of reversal of hepatic fibrosis and inflammation in patients with TDT receiving DFX
Endocrinopathy	Endocrine tests (age >10 yr) every 6–12 mo, or every 3–6 mo as needed in patients with abnormality§	Treatment per local standards Evidence of reversal of endocrine dysfunction in patients with TDT receiving combination ICT Lower prevalence in patients with NTDT receiving HU or ICT
Growth and pubertal delay	Children (age <18 yr) — weight measurement at every visit, standing and sitting height every 6 mo and bone age every 12 mo if delayed puberty or growth Children (age 10–17 yr) — Tanner staging every 12 mo Adults (age ≥18 yr) — weight measurement at every visit, routine assessment for infertility, secondary hypogonadism, and impotence	Treatment per local standards
Osteoporosis and bone disease	BMD (age >10 yr) — every 24 mo or every 12 mo as needed in patients with abnormality	Treatment per local standards Treatment benefit in several trials with various bisphosphonates Lower prevalence among patients with NTDT receiving transfusions, HU, or ICT
Facial and bone deformity	Physical examination at every visit, especially in inadequately transfused patients with TDT	Treatment per local standards
Extramedullary hematopoietic pseudotumors	Physical examination and imaging with clinical suspicion, especially in patients with NTDT, splenectomized patients, and those with Hb <10 g/dl	Treatment benefit in several studies with hypertransfusion, HU, irradiation, or surgery Lower prevalence in patients with NTDT receiving transfusions or HU
Leg ulcers	Skin inspection at every visit, especially in adults, patients with NTDT, splenectomized patients, or those with Hb <10 g/dl	Treatment benefit in several studies with topical measures, pentoxifylline, HU, hyperoxygenation, or transfusion Lower prevalence in patients with NTDT receiving transfusions or HU
Hepatosplenomegaly	Physical examination at every visit	Splenectomy, if clinical symptoms of splenomegaly present

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Table 1. (Continued.)

Complication	Monitoring†	Management or Prevention‡
Hyperbilirubinemia and gallstones	Laboratory testing and imaging with clinical suspicion	Treatment per local standards Lower prevalence in NTDT patients receiving transfusions
Proteinuria and GFR abnormalities	Laboratory testing and imaging with clinical suspicion, especially in patients with severe anemia or iron overload	Treatment per local standards
Infections	Laboratory testing and imaging with clinical suspicion, especially in splenectomized patients HCV, HBV, and HIV tests every 12 mo in regularly transfused patients	Treatment per local standards
Hematologic and other cancers	Laboratory testing and imaging with clinical suspicion, especially in adults	Treatment per local standards
Iron chelator–related adverse events	Monitoring per prescribing information for iron chelator	Prevention and treatment per prescribing information for iron chelator
Infertility or pregnancy	Fertility assessment: menstrual history, antral follicle count, antimullerian hormone measurement Before pregnancy: counseling on the risk of having affected children; iron overload, hepatic function, cardiac function, endocrine function, calcium, vitamin D, bone health, viral status (HBV, HCV, HIV) and extended infection screening, red-cell antibodies; thrombotic risk assessment; gall bladder ultrasound Assessment during pregnancy: iron overload (serum ferritin measurement every 1 mo); cardiac, hepatic, and thyroid function (every trimester); gestational diabetes (at 16 and 28 wk); serial ultrasound (every 1 mo) for growth retardation; prenatal diagnosis	Attaining pregnancy: induction of ovulation or spermatogenesis in patients with hypogonadism, elective cryopreservation of oocytes or ovarian tissue, assisted reproductive technology Before pregnancy: folic acid, thyroid-function optimization, ICT intensification During pregnancy: discontinuation of DFX/DFP (DFO may be used in the second and third trimesters, especially in patients with cardiac symptoms or rapid increase in serum ferritin), ACE inhibitors, vitamin C, HU, hormone replacement therapy, bisphosphonates (discontinuation 6 mo before pregnancy), interferon or ribavirin, warfarin (switched to heparins), oral hypoglycemic agents (switched to insulin); resumption of calcium, vitamin D; maintenance of Hb level at >10 g/dl; prophylactic anticoagulation with aspirin or LMWH for women considered at high risk At delivery: vaginal birth vs. cesarean section depends on pelvic status and cephalopelvic disproportion; epidural anesthesia in case of cesarean section After delivery: restart ICT (DFO only if breast-feeding), bisphosphonates; resumption of calcium, vitamin D; avoidance of breast-feeding if positive for HIV, HBV, or HCV; prophylactic anticoagulation with LMWH for women at high risk

* The information presented in the table is from the following sources: Cappellini et al.,[22] Taher et al.,[23] Taher et al.,[29] Taher and Cappellini,[48] and Carlberg et al.[50] ACE denotes angiotensin-converting enzyme, ALT alanine aminotransferase, AST aspartate aminotransferase, BMD bone mineral density, DAA direct-acting antiviral drug, DFO deferoxamine, DFP deferiprone, DFX deferasirox, ECG electrocardiogram, GFR glomerular filtration rate, HAV hepatitis A virus, Hb hemoglobin, HBV hepatitis B virus, HCC hepatocellular carcinoma, HCV hepatitis C virus, HIV human immunodeficiency virus, HU hydroxyurea, ICT iron-chelation therapy, LMWH low-molecular-weight heparin, LVEF left-ventricular ejection fraction, NTDT non–transfusion-dependent β-thalassemia, RHC right-heart catheterization, TDT transfusion-dependent β-thalassemia, TRV tricuspid-valve regurgitant jet velocity, and ULN upper limit of the normal range.
† These represent common measures for routine or ad hoc screening. Confirmatory diagnosis should follow local standards.
‡ Management of anemia and iron overload may help prevent most complications.
§ Endocrine measurements include thyrotropin, calcium, phosphate, vitamin D, and parathyroid hormone (as indicated); luteinizing hormone, follicle-stimulating hormone, testosterone, estradiol, gonadotropin-releasing hormone (as indicated in cases of abnormal sexual development); and fasting blood glucose and an oral glucose tolerance test (as indicated).

lifelong regular transfusion therapy for such patients. Data from studies of new therapies (see below) targeting anemia in this patient population are awaited. All patients with non–transfusion-dependent β-thalassemia should be monitored for iron overload according to serum ferritin or liver iron measurements, starting at the age of 10 years, when iron-related complications begin to appear. For patients with serum ferritin levels of 800 ng per milliliter or higher or a liver iron concentration of 5 mg per gram or higher, iron-chelation therapy is recommended, with target ferritin and liver iron concentrations of 300 ng per milliliter or lower and 3 mg per gram or

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Table 2. Ongoing Clinical Assessment of New Treatments for β-Thalassemia.*

Agent	Mechanism of Action	Trial	Study Population†	Key Efficacy End Points	Available Data
CTX001	Genome editing disrupts *BCL11A* and increase HbF Autologous CD34+ HSPCs are mobilized with G-CSF and plerixafor, then collected and edited with CRISPR-Cas9 using a guide RNA specific for the erythroid-specific enhancer region of *BCL11A* Product is infused after myeloablative busulfan conditioning	CLIMB THAL-111 (ClinicalTrials.gov number NCT03655678): phase 1–2, open-label	TDT, age 12–35 yr, eligible for HSCT but no matched sibling donor (n=45, estimated)	Transfusion reduction or independence ≥6 mo Engraftment, gene editing Change in Hb, HbF Change in quality of life, patient-reported outcomes Change in SF, LIC, MIC, ICT	Initial data for 5 patients: Engraftment of neutrophils and platelets at medians of 32 and 27 days, respectively Increases in total Hb and HbF over time in all patients Patients ceased receiving transfusions soon after CTX001 infusion, with last transfusion occurring between 0.9 and 1.9 mo after CTX001 infusion The first patient who received CTX001 has remained transfusion-free for >15 mo Safety profile was generally consistent with busulfan myeloablation and autologous HSCT[76,77]
ST-400	Genome editing to disrupt *BCL11A* and increase HbF Autologous CD34+ HSPCs are mobilized with G-CSF and plerixafor, then collected and transfected ex vivo with mRNA encoding ZFN with binding sites flanking the GATA-binding erythroid-specific enhancer region of *BCL11A* Product is infused after myeloablative busulfan conditioning	THALES (NCT03432364): phase 1–2, open-label	TDT, age 18–40 yr (n=6, estimated)	Transfusion reduction Change in Hb, HbF	Initial data with 3 patients: Patient 1 (β^0/β^0): prompt hematopoietic reconstitution, increase in HbF, transfusion-free for 6 wk, then intermittent transfusions; hypersensitivity during infusion Patient 2 (β^+/β^+): increase in HbF levels through 90 days; further clinical assessment awaited Patient 3 (β^0/β^+): stem cells were edited, infusion of the "manufactured" product was awaited Safety profile was otherwise generally consistent with busulfan myeloablation and autologous HSCT[78]
Luspatercept (ACE-536)	Subcutaneous, recombinant fusion protein that binds to select TGF-β superfamily ligands and enhances late-stage erythropoiesis Increased erythroid maturation and hemoglobin levels in mouse models and patients with NTDT in an open-label, phase 2 study	BEYOND (NCT03342404): phase 2, randomized (2:1), double-blind, placebo-controlled	NTDT, age ≥18 yr, Hb ≤10 g/dl (n=145, actual)	Hb increase ≥1.0 g/dl Change in patient-reported outcomes Change in SF, LIC, ICT	—

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Mitapivat (AG-348)	Oral, small-molecule, allosteric activator of the red-cell–specific form of pyruvate kinase Increased ATP levels, reduced markers of ineffective erythropoiesis, and improved anemia, red-cell survival, and indexes of iron overload in mouse models	NCT03692052: phase 2, open-label	NTDT (including α-thalassemia), age ≥18 yr, Hb ≤10 g/dl (n=20, actual)	Hb increase ≥1.0 g/dl Changes in markers of hemolysis and ineffective erythropoiesis	Interim data for β-thalassemia: Hb increase ≥1.0 g/dl in 8 of 9 patients at 12 wk Favorable changes in markers of erythropoiesis and hemolysis AEs in >3 patients: insomnia, dizziness, cough, dyspepsia, fatigue, headache, nasal congestion, nausea, and upper respiratory tract infection[79]
VIT-2763	Oral ferroportin inhibitor Restricted iron availability, ameliorated anemia, and reversed dysregulated iron homeostasis in mouse models	VITHAL (NCT04364269): phase 2, randomized, double-blind, placebo-controlled	NTDT, age 12–65 yr, Hb ≤11 g/dl (n=36, estimated)	Changes in Hb, SF, serum transferrin, and TSAT	—
TMPRSS6-LRx	Subcutaneous, antisense oligonucleotides down-regulating TMPRSS6 (metalloprotease with key role in hepcidin expression) Stimulated hepcidin, reduced iron burden, and improved ineffective erythropoiesis and red-cell survival in mouse models	NCT04059406: phase 2, randomized, open-label	NTDT, age ≥18 yr, Hb 6–10 g/dl, LIC 3–20 mg/g (n=36, estimated)	Hb increase ≥1.0 g/dl LIC decrease ≥1 mg/g	—

* Data are from the following sources: Suragani et al.,[62] Suragani et al.,[63] Piga et al.,[65] Psatha et al.,[71] Antoniani et al.,[72] Guo et al.,[73] Manolova et al.,[74] and Matte et al.[75] The list of drugs under investigation is not exhaustive; it includes key agents that are under investigation in clinical trials for the treatment of β-thalassemia. AEs denotes adverse events, CRISPR clustered regularly interspaced short palindromic repeats, G-CSF granulocyte colony-stimulating factor, HbF fetal hemoglobin, HSCT hematopoietic stem-cell transplantation, HSPCs hematopoietic stem and progenitor cells, LIC liver iron concentration, MIC myocardial iron concentration, mRNA messenger RNA, SF serum ferritin, TGF-β transforming growth factor β, TMPRSS6 transmembrane serine protease 6, TSAT transferrin saturation, and ZFN zinc-finger nuclease.

† Enrollment numbers are from the ClinicalTrials.gov website as of November 5, 2020.

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lower, respectively.[23] Although data from studies with deferoxamine and deferiprone are available,[60] deferasirox is the only iron chelator specifically approved for this population on the basis of data from a randomized, phase 2 trial showing significant reductions in serum ferritin and liver iron concentrations over a 2-year period of therapy.[61]

LUSPATERCEPT THERAPY

Luspatercept (ACE-536) is the most recently approved agent (in the United States and Europe) for the treatment of adults with transfusion-dependent β-thalassemia. It is a recombinant fusion protein comprising a modified extracellular domain of the human activin receptor type IIB fused to the Fc domain of human IgG1. Together, the domains bind to select transforming growth factor β superfamily ligands, block SMAD2/3 signaling, and enhance erythroid maturation.[62-64] On the basis of encouraging data in a phase 2 study,[65] a recent phase 3, double-blind trial (BELIEVE) involving adults with transfusion-dependent β-thalassemia who were randomly assigned to receive subcutaneous luspatercept at a dose of 1.00 to 1.25 mg per kilogram of body weight (224 patients) or placebo (112 patients) every 3 weeks showed that luspatercept reduced the transfusion burden by at least 33% (in 21.4% of the luspatercept group vs. 4.5% of the placebo group) over a fixed 12-week period.[66] Parallel reductions in serum ferritin levels were also observed, with no clinically meaningful changes in liver or myocardial iron concentrations. Adverse events, consisting of transient bone pain, arthralgia, dizziness, hypertension, and hyperuricemia, were more common with luspatercept than with placebo. Higher rates of thrombosis were noted in the luspatercept-treated patients. Although these thrombotic events occurred mainly in patients with known risk factors, monitoring patients for signs and symptoms of thrombotic events is recommended. Luspatercept is now gradually being integrated in local management protocols for transfusion-dependent β-thalassemia. Data on long-term use and use in children are awaited.

HEMATOPOIETIC STEM-CELL TRANSPLANTATION

Disease-free survival rates exceeding 90% have been reported for hematopoietic stem-cell transplantation (HSCT) in children with transfusion-dependent β-thalassemia who have favorable risk profiles and matched sibling donors. Improvements in transplantation protocols and management of transplantation-related complications have also allowed for the use of matched unrelated donors, haploidentical related donors, and umbilical-cord blood as the stem-cell source. Outcome rates vary geographically, and these approaches should be considered only at centers with expertise.[67,68]

GENE THERAPY

Gene therapy is based on the concept of correcting the defective production of β-globin chains by isolating hematopoietic stem cells from a person with β-thalassemia and transducing them with viruses to introduce exogenous β-like–globin transgenes that can allow for gene expression. The first such gene therapy, betibeglogene autotemcel (LentiGlobin BB305), has received conditional marketing authorization in Europe for patients with transfusion-dependent β-thalassemia who are 12 years of age or older, have a non–β^0/β^0 genotype, and are eligible for a transplant but do not have a matched sibling donor. The approval was based on data from two phase 1–2 studies involving 22 patients who were reinfused with cells transduced ex vivo with the LentiGlobin BB305 vector, which encodes HbA with a T87Q amino acid substitution, a hemoglobin variant that resists sickling.[69] Fifteen of the 22 patients stopped receiving transfusions after gene therapy (12 of 13 patients with a non–β^0/β^0 genotype and 3 of 9 patients with a β^0/β^0 genotype), and the remaining patients received a lower annualized red-cell volume and a lower number of transfusions than before gene therapy. Treatment-related adverse events were typical of those associated with autologous HSCT.

Final data from two ongoing phase 3 trials involving children and adults with β^0/β^0 or non–β^0/β^0 transfusion-dependent β-thalassemia are awaited (ClinicalTrials.gov numbers, NCT02906202 and NCT03207009). A few other vectors and gene therapy approaches have also been evaluated. In a phase 1–2 trial involving patients with transfusion-dependent β-thalassemia and β^0 or severe β^+ mutations, intrabone administration of hematopoietic stem cells transduced with the β-globin–expressing (GLOBE) lentiviral vector resulted in

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a reduced requirement for transfusions in three adults and complete independence from transfusions in three of four evaluated children.[70]

ONGOING CLINICAL DEVELOPMENT

In place of gene therapy, recent approaches have been developed to directly correct genetic mutations or to disrupt specific DNA sequences in the genome (genome editing). Two engineered nucleases — zinc-finger nucleases (ZFNs) and clustered regularly interspaced short palindromic repeats linked to Cas9 nucleases (CRISPR-Cas9) — are being evaluated in transfusion-dependent patients.[71,72] Autologous CD34+ cells are mobilized, collected, and edited to disrupt the erythroid-specific enhancer region of *BCL11A* and increase HbF production. The product is infused in patients after myeloablative conditioning. Two ongoing clinical trials are assessing transfusion requirements in patients with transfusion-dependent β-thalassemia who are undergoing treatment with the products CTX001 (CRISPR-Cas9) or ST-400 (ZFNs) (Table 2).

Luspatercept is also being evaluated for its effect on hemoglobin levels in an ongoing trial (BEYOND) involving adults with non–transfusion-dependent β-thalassemia. Several other agents are being evaluated for a similar effect in this patient population. Whether these agents directly target iron dysregulation (VIT-2763 and TMPRSS6-LRx)[73,74] or ineffective erythropoiesis (mitapivat [AG-348]),[75] the intended effect is alleviation of anemia and prevention of primary iron overload, given the bidirectional relationship between these two complications. Combinations of these agents or combinations of one or more of them with iron-chelation therapy may be needed to fully control or reverse the underlying disease process in non–transfusion-dependent β-thalassemia (Table 2).

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