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Edward J. Benz Jr	
<p>Thalassemia is a heterogeneous group of inherited anemias having in common defective biosynthesis of one or more of the globin chain subunits of human hemoglobin. Their origins lie in inherited mutations that impair the expression of the affected globin genes. Their pathophysiology arises from the consequent insufficiency of hemoglobin production and the imbalance in the production of globin chains resulting in the accumulation of insoluble unpaired chains. These precipitate and damage or destroy developing erythroblasts and erythrocytes producing ineffective erythropoiesis and hemolytic anemia. Treatment of severe cases requires lifelong transfusion support with iron chelation therapy.</p>	
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<p>Epidemiology is the practical tool to provide information on which policy makers should base planning of services. Epidemiological data for thalassemia is based on inaccurate and often conflicting measurements. This study attempts to demonstrate with examples the sources of inaccuracy and confusion. The Thalassemia International Foundation (TIF) suggests that congenital disorders, for which increasing complications and premature death are avoidable through appropriate treatment and follow-up, should be given priority based on accurate data and patient registries. Moreover, only accurate information about this issue, especially for developing countries, will move national health resources in the right direction.</p>	
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<p>Thalassemia syndromes are common monogenic disorders and represent a significant health issue worldwide. In this review, the authors elaborate on fundamental genetic knowledge about thalassemias, including the structure and location of globin genes, the production of hemoglobin during development, the molecular lesions causing α-, β-, and other thalassemia syndromes, the genotype-phenotype correlation, and the genetic modifiers of these conditions. In addition, they briefly discuss the molecular techniques applied for diagnosis and innovative cell and gene therapy strategies to cure these conditions.</p>	

Fetal Hemoglobin Regulation in Beta-Thalassemia

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Henry Y. Lu, Stuart H. Orkin, and Vijay G. Sankaran

β -thalassemia is caused by mutations that reduce β -globin production, causing globin chain imbalance, ineffective erythropoiesis, and consequent anemia. Increased fetal hemoglobin (HbF) levels can ameliorate the severity of β -thalassemia by compensating for the globin chain imbalance. Careful clinical observations paired with population studies and advances in human genetics have enabled the discovery of major regulators of HbF switching (i.e. BCL11A, ZBTB7A) and led to pharmacological and genetic therapies for treating β -thalassemia patients. Recent functional screens using genome editing and other emerging tools have identified many new HbF regulators, which may improve therapeutic HbF induction in the future.

Clinical Classification, Screening, and Diagnosis in Beta-Thalassemia and Hemoglobin E/Beta-Thalassemia

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Morgan Pines and Sujit Sheth

This article reviews the classification of beta-thalassemia syndromes, correlating clinical severity and genotype in the earlier classification, and broadening it recently based on clinical severity and transfusion status. The classification is dynamic, and individuals may progress from transfusion-independent to transfusion-dependent. Early and accurate diagnosis prevents delays in instituting treatment and comprehensive care, and precludes inappropriate and potentially harmful interventions. Screening can inform risk in an individual and subsequent generations when partners may be carriers as well. This article discusses the rationale for screening of the at-risk population. In the developed world, a more precise genetic diagnosis must be considered.

The Clinical Phenotypes of Alpha Thalassemia

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Ashutosh Lal and Elliott Vichinsky

Clinical manifestations of α -thalassemia range from no symptoms to severe transfusion-dependent anemia. Alpha thalassemia trait is deletion of 1 to 2 α -globin genes, whereas α -thalassemia major (ATM; Barts hydrops fetalis) is the deletion all 4 α genes. All other genotypes of intermediate severity are categorized as HbH disease, a vastly heterogeneous group. Clinical spectrum is classified as mild, moderate, and severe by symptoms and need for intervention. Anemia in prenatal period may be fatal without intrauterine transfusions. New therapies to modify HbH disease or provide cure for ATM are under development.

Pathogenic Mechanisms in Thalassemia I: Ineffective Erythropoiesis and Hypercoagulability

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Rayan Bou-Fakhredin, Stefano Rivella, Maria Domenica Cappellini, and Ali T. Taher

Erythropoiesis is the physiological process that results in the production of red blood cells (RBCs). In conditions of pathologically altered erythropoiesis or ineffective erythropoiesis, as in the case of β -thalassemia, the reduced ability of erythrocytes to differentiate, survive and deliver oxygen

stimulates a state of stress that leads to the ineffective production of RBCs. We herein describe the main features of erythropoiesis and its regulation in addition to the mechanisms behind ineffective erythropoiesis development in β -thalassemia. Finally, we review the pathophysiology of hypercoagulability and vascular disease development in β -thalassemia and the currently available prevention and treatment modalities.

Pathogenic Mechanisms in Thalassemia II: Iron Overload **353**

Tomas Ganz and Elizabeta Nemeth

Iron overload remains a lethal complication of β -thalassemia and other anemias caused by ineffective erythropoiesis. This review discusses the pathogenetic mechanisms of iron overload in thalassemia, at organismal, cellular, and molecular levels.

Clinical Complications and Their Management **365**

Rayan Bou-Fakhredin, Irene Motta, Maria Domenica Cappellini, and Ali T. Taher

The diversity of disease-related complications among patients with β -thalassemia is complicated by the wide spectrum of genotypes and clinical risk factors. The authors herein present the different complications seen in patients with β -thalassemia, the pathophysiology underlying these complications and their management.

Clinical Challenges with Iron Chelation in Beta Thalassemia **379**

Janet L. Kwiatkowski

Conventional therapy for severe thalassemia includes regular red cell transfusions and iron chelation therapy to prevent and treat complications of iron overload. Iron chelation is very effective when appropriately used, but inadequate iron chelation therapy continues to contribute to preventable morbidity and mortality in transfusion-dependent thalassemia. Factors that contribute to suboptimal iron chelation include poor adherence, variable pharmacokinetics, chelator adverse effects, and difficulties with precise monitoring of response. The regular assessment of adherence, adverse effects, and iron burden with appropriate treatment adjustments is necessary to optimize patient outcomes.

Fertility and Pregnancy in Women with Transfusion-Dependent Thalassemia **393**

Farzana A. Sayani, Sylvia T. Singer, Katie T. Carlberg, and Elliott P. Vichinsky

Because women with transfusion-dependent thalassemia are seeking pregnancy, ensuring the best outcomes for both mother and baby require concerted and collaborative efforts between the hematologist, obstetrician, cardiologist, hepatologist, and genetic counselor among others. Proactive counseling, early fertility evaluation, optimal management of iron overload and organ function, and application of advances in reproductive technology and prenatal screening are important in ensuring a healthy outcome. Many unanswered questions remain requiring further study, including fertility preservation and best timing to implement it, in light of advances in curative options, chelation therapy during pregnancy, and indications and duration of anticoagulation.

Hematopoietic Stem Cell Transplantation in Thalassemia

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Mattia Algeri, Mariachiara Lodi, and Franco Locatelli

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only consolidated, potentially curative treatment for patients with transfusion-dependent thalassemia major. In the past few decades, several new approaches have reduced the toxicity of conditioning regimens and decreased the incidence of graft-versus-host disease, improving patients' outcomes and quality of life. In addition, the progressive availability of alternative stem cell sources from unrelated or haploidentical donors or umbilical cord blood has made HSCT a feasible option for an increasing number of subjects lacking an human leukocyte antigen (HLA)-identical sibling. This review provides an overview of allogeneic hematopoietic stem cell transplantation in thalassemia, reassesses current clinical results, and discusses future perspectives.

Gene Therapy and Gene Editing for β -Thalassemia

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Georgios E. Christakopoulos, Rahul Telange, Jonathan Yen, and Mitchell J. Weiss

After many years of intensive research, emerging data from clinical trials indicate that gene therapy for transfusion-dependent β -thalassemia is now possible. Strategies for therapeutic manipulation of patient hematopoietic stem cells include lentiviral transduction of a functional erythroid-expressed β -globin gene and genome editing to activate fetal hemoglobin production in patient red blood cells. Gene therapy for β -thalassemia and other blood disorders will invariably improve as experience accumulates over time. The best overall approaches are not known and perhaps not yet established. Gene therapy comes at a high cost, and collaboration between multiple stakeholders is required to ensure that these new medicines are administered equitably.

Emerging Therapies in β -Thalassemia

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Rayan Bou-Fakhredin, Kevin H.M. Kuo, and Ali T. Taher

Advances in understanding the underlying pathophysiology of β -thalassemia have enabled efforts toward the development of novel therapeutic modalities. These can be classified into three major categories based on their ability to target different features of the underlying disease pathophysiology: correction of the α/β globin chain imbalance, targeting ineffective erythropoiesis, and targeting iron dysregulation. This article provides an overview of these different emerging therapies that are currently in development for β -thalassemia.