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Review

# Alpha-thalassemia: A practical overview

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ABSTRACT

α-Thalassemia is an inherited blood disorder characterized by decreased synthesis of α-globin chains that results in an imbalance of α and β globin and thus varying degrees of ineffective erythropoiesis, decreased red blood cell (RBC) survival, chronic hemolytic anemia, and subsequent comorbidities. Clinical presentation varies depending on the genotype, ranging from a silent or mild carrier state to severe, transfusion-dependent or lethal disease. Management of patients with α-thalassemia is primarily supportive, addressing either symptoms (eg, RBC transfusions for anemia), complications of the disease, or its transfusion-dependence (eg, chelation therapy for iron overload). Several novel therapies are also in development, including curative gene manipulation techniques and disease modifying agents that target ineffective erythropoiesis and chronic hemolytic anemia. This review of α-thalassemia and its various manifestations provides practical information for clinicians who practice beyond those regions where it is found with high frequency.

## 1. Introduction

The thalassemias are inherited, autosomal recessive disorders of hemoglobin (Hb) synthesis characterized by a variety of molecular defects and are among the most common genetic diseases worldwide [1–3]. The principal forms, α- and β-thalassemia, result from mutations in globin genes that lead to a deficit or qualitative change in the production of the α-globin and β-globin chains of adult Hb, respectively [4].

The global disease burden of thalassemia is substantial, with 5% to 20% of the world population carrying one or more α-thalassemia mutations, and ≈1.5% carrying one or more β-thalassemia mutations [5–7]. Prevalence rates vary among regions but are highest in tropical and subtropical countries, particularly in Southeast Asia and the Mediterranean [8]. α-Thalassemia has almost reached fixation (frequency has reached 100% in the population) in some parts of southern Asia, with 80% to 90% of the population being carriers [9–11]. The thalassemias are more common in areas where falciparum malaria has been widespread and endemic, possibly conferring a protective advantage in malarial environments [12–16]. The total burden of thalassemia on economic and healthcare systems is not currently known but is understood to be increasing, not only in countries with high prevalence where more patients are surviving and living longer lives [17], but also where prevalence is increasing due to immigration and demographic transitions [3,18]. Although there are significant gaps in our knowledge of the prevalence and health burden of α-thalassemia, the increasing speed and decreasing cost of genetic testing and other screening methods may aid in the goal of treatment and future prevention.

Of the hemoglobinopathies, α-thalassemia, with its complex mutations, is particularly challenging to clinicians. Clinically diverse forms of the disease present across a wide spectrum of phenotypes, ranging from asymptomatic or mild carrier states to severe, transfusion-dependent or lethal types, with a broad range of clinical manifestations in between.

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This overview aims to describe the disease and its various manifestations to clinicians who practice in regions where it is relatively rare. We review the molecular genetics and genotype/phenotype correlations to establish a firm knowledge base and promote the recognition, differential diagnosis, counseling, and clinical management of α-thalassemia. New information regarding emerging therapies and agents in development is also provided. It is worth noting that overall, evidence-based observations in α-thalassemia are relatively limited, with several aspects of diagnosis and management extrapolated from studies of β-thalassemia. In this review, we use our experience in treating the disease over the past few decades to fill such evidence gaps.

## 2. Molecular understanding

### 2.1. Molecular genetics of normal hemoglobin

Human Hb synthesis is directed by an α-globin gene cluster (containing 1 embryonic ζ gene and a linked pair of fetal/adult α genes) located on chromosome 16 and a β-globin gene cluster containing 1 embryonic ε gene, 2 embryonic/fetal γ genes, and the adult δ and β genes (1 each) located on chromosome 11 (Fig. 1A) [19–22].

### 2.2. Normal hemoglobin synthesis

Hemoglobin is a tetrameric protein consisting of 2 homodimers of globin subunits, each comprising a globin chain conjugated with a heme moiety having a liganded iron atom at the center that binds one oxygen

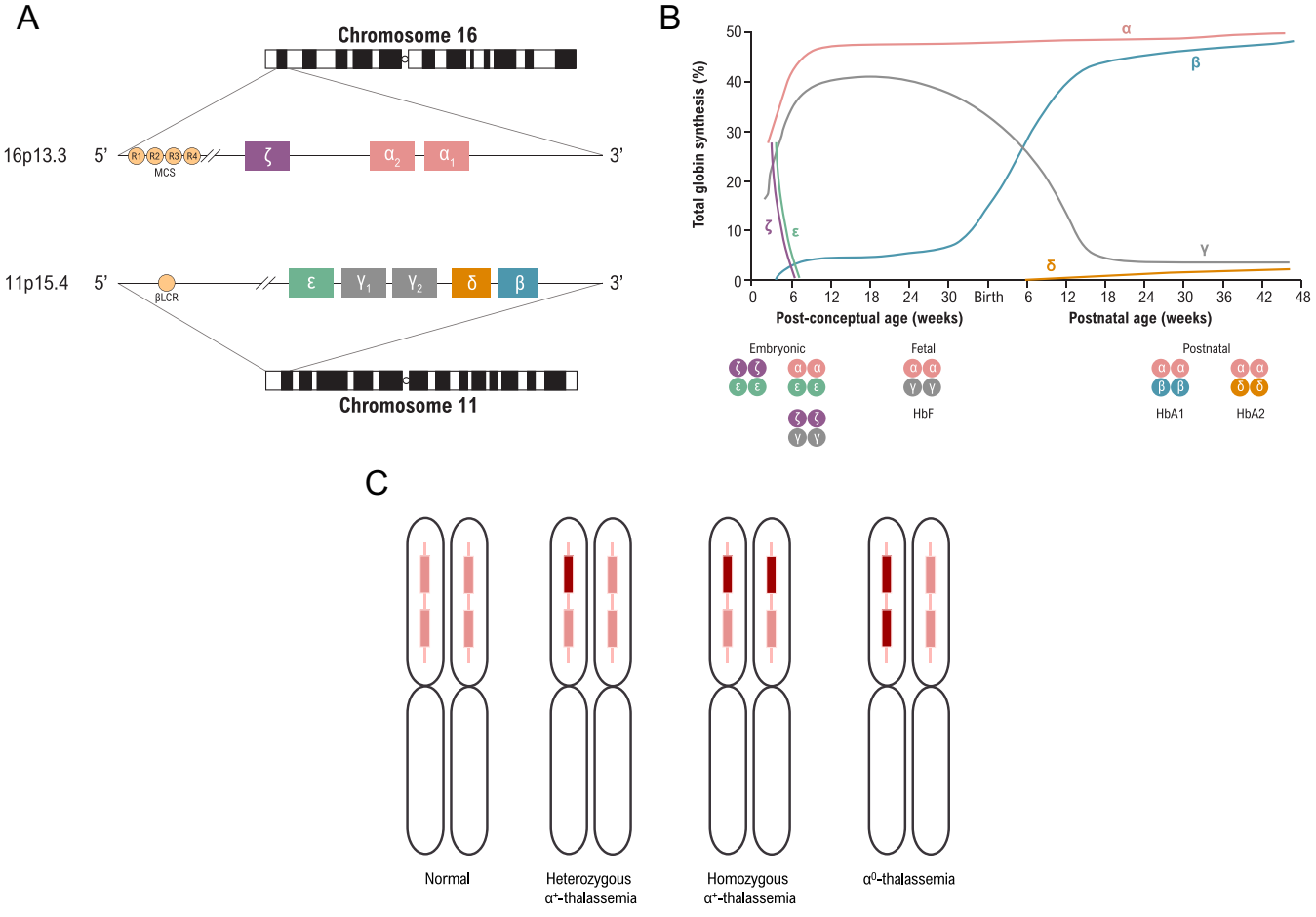


**Fig. 1. Human globin synthesis. (A)** Chromosomal location and organization of the α- and β-globin gene clusters. The α- and β-globin gene clusters are located on chromosomes 16p13.3 and 11p15.4, respectively. The ζ-globin, $\alpha_2$-globin, and $\alpha_1$-globin genes are driven by 4 conserved enhancer elements (MCS-R1 through MCS-R4), and the ε-globin, $\gamma_1$-globin, $\gamma_2$-globin, δ-globin, and β-globin genes are driven by an enhancer cluster, the locus control region (βLCR). Adapted from Farashi S, et al. Blood Cells Mol Dis 2018;70:43–53 with kind permission from Elsevier. **(B)** Hemoglobin switching at the α- and β-globin loci. During primitive erythropoiesis in the yolk sac, the embryonic ζ-globin (from the α-globin locus) and ε-globin (from the β-globin locus) genes are expressed until approximately 8 weeks' gestation, when these genes are silenced and there is a maturational switch to α- and γ-globin expression during fetal life. A second switch from γ- to β-globin occurs at birth. Embryonic Hb ($\zeta_2\gamma_2$ [Hb Portland], $\zeta_2\varepsilon_2$ [Hb Gower 1], and $\alpha_2\varepsilon_2$ [Hb Gower 2]) is produced through the yolk sac stage of development, when ζ- and ε-globin chain production stop, resulting in the formation of fetal Hb ($\alpha_2\gamma_2$ [HbF]). As the fetus approaches birth, γ-globin production slowly decreases as β-globin production increases. Shortly after birth, β- and δ-globin production have replaced γ-globin production, resulting in the production of adult Hb ($\alpha_2\beta_2$ [HbA1] and $\alpha_2\delta_2$ [HbA2]). This figure was first published in Bunn HF, et al. Human Hemoglobins. Philadelphia, PA: WB Saunders; 1977; adapted with kind permission from Elsevier. **(C)** Deletion or inactivation of one of the α-globin genes in a linked pair is designated $\alpha^+$-thalassemia. $\alpha^+$-Thalassemia is "heterozygous" when on only one of the two chromosome 16 and "homozygous" when on both. Deletion or inactivation of both α-globin genes in a linked pair on the same chromosome 16 is referred to as $\alpha^0$-thalassemia. *Abbreviations:* βLCR, β-locus control region; Hb, hemoglobin; $\alpha_1$, fetal/adult α-gene 1; $\alpha_2$, fetal/adult α-gene 2; β, postnatal β-gene; δ, postnatal δ-gene; ε, embryonic ε-gene; $\gamma_1$, embryonic/fetal γ-gene 1; $\gamma_2$, embryonic/fetal γ-gene 2; ζ, embryonic ζ-gene; MCS, multispecies conserved sequence.

molecule [19,22,23]. Expression of human globin genes switches during transition from embryo to fetus to adult (Fig. 1B) [24,25]. Thus, the composition of Hb tetramers also changes from embryonic hemoglobins $\zeta_2\gamma_2$ (Hb Portland), $\zeta_2\varepsilon_2$ (Hb Gower 1), and $\alpha_2\varepsilon_2$ (Hb Gower 2) embryonic Hb; to $\alpha_2\gamma_2$ (HbF) fetal Hb; and then to $\alpha_2\beta_2$ (HbA1) and $\alpha_2\delta_2$ (HbA2) adult Hb. The usual proportion of Hb types in normal adults is 95% to 98% HbA1 ($\alpha_2\beta_2$), 2% to 3% HbA2 ($\alpha_2\delta_2$), and < 2% HbF ($\alpha_2\gamma_2$) [17,26,27].

### 2.3. α-Thalassemia mutations

Normal individuals carry 4 α-globin genes ($\alpha_2\ \alpha_1$ / $\alpha_2\ \alpha_1$). α-Thalassemia is caused by deletional (−) or nondeletional ($\alpha^T$) mutations in the α-globin genes, which result in impaired α-globin production. Approximately 130 different molecular defects are known to cause α-thalassemia, mainly large fragment deletions [28]. For a complete updated list, visit the Globin Gene Server Web Site (https://globin.bx.psu.edu/hbvar/menu.html).

Deletion or inactivation of one of the α-globin genes in the linked pair is designated $\alpha^+$-thalassemia (Fig. 1C); heterozygous $\alpha^+$-thalassemia when on one chromosome 16 (− α / α α), homozygous $\alpha^+$-thalassemia when on both chromosome 16 (− α / − α). Deletion or inactivation of both α-globin genes in the linked pair on the same chromosome 16 is referred to as $\alpha^0$-thalassemia (− − / α α) [27]. >40 $\alpha^0$-thalassemia mutations have been found and are usually designated by the region where the condition was first discovered; the most common $\alpha^0$-thalassemia deletional mutations include the Southeast Asia (− $-^{SEA}$ / α α), Filipino (− $-^{FIL}$ / α α), and Mediterranean (− $-^{MED}$ / α α) mutations [29]. Hemoglobin H (HbH) disease occurs when 2 α-globin genes are deleted on one chromosome 16 and a third is either deleted, inactivated, or changed qualitatively on the other chromosome 16, leaving only one functional α-globin gene. Hemoglobin Barts (Hb Barts) hydrops fetalis syndrome occurs when all 4 α-globin genes are deleted or inactivated (homozygous $\alpha^0$-thalassemia) [27].

### 2.4. α-Thalassemia heritability

The genetics of α-thalassemia are complex. Each person inherits two α-globin genes from each parent. If both parents are each missing one or more α-globin genes, their children are at risk of having α-thalassemia trait, HbH disease, or Hb Barts hydrops fetalis syndrome. Precise risk depends on how many genes are deleted or inactivated, which α-globin gene(s) ($\alpha_2$ or $\alpha_1$) is(are) affected, and whether the deleted/inactivated genes are on one or both chromosomes. For example, individuals with − − / α α ($\alpha^0$-thalassemia) are at greater risk of having severely affected children compared to those with − α / − α (homozygous α + −thalassemia). Therefore, molecular diagnosis in cases of $\alpha^+$-thalassemia and $\alpha^0$-thalassemia is an important consideration in reproductive counseling [27].

## 3. Classification

### 3.1. Genotype-phenotype correlations

The number of functional α-globin genes determines the extent of α-globin/non–α-globin chain imbalance, and thus, the clinical severity of α-thalassemia. Because two-thirds of α-globin synthesis come from the $\alpha_2$ gene, mutations affecting the $\alpha_2$ gene are typically associated with a more severe reduction of α-globin synthesis [30,31]. Reduced production (<70% of normal) of α-globin chains in the fetus results in an excess of γ-globin chains, which then form insoluble γ tetramers (Hb Barts) [28]. In adults, surplus β-globin chains form insoluble β tetramers (HbH). Both HbH and Hb Barts bind oxygen with high affinity, do not have heme-heme interactions, and cannot transport/release oxygen to tissues effectively [32]. In addition, the instability of HbH can lead to the production of inclusion bodies in red blood cells (RBCs), resulting in reduced red cell survival and a varying degree of hemolytic anemia [33,34]. The amount of α-globin produced impacts the amount of β-globin or γ-globin available to form HbH or Hb Barts. Newborns who inherit HbH disease (one functional α-globin gene) have 20% to 40% of Hb Barts at birth [32,35].

### 3.2. Clinical forms and definitions

α-Thalassemia presents in 3 carrier states (heterozygous or homozygous $\alpha^+$- and $\alpha^0$-thalassemia) and 2 clinically relevant forms (HbH disease and Hb Barts hydrops fetalis syndrome; Fig. 2). Persons with heterozygous $\alpha^+$-thalassemia (silent carrier or α-thalassemia minima; 3 functional genes) are either clinically silent (asymptomatic, with normal red cell parameters, and normal HbA and HbF) or show normal HbA and HbF with mild hematological changes (eg, mild anemia with low mean corpuscular volume [MCV]) [27,36,37]. Persons with $\alpha^0$-thalassemia or homozygous $\alpha^+$-thalassemia (α-thalassemia trait or α-thalassemia minor; 2 functional genes) are usually asymptomatic but have a mild microcytic anemia with normal proportions of HbA and HbF, depending on the amount of α-globin produced [27,37].

Individuals with HbH disease (α-thalassemia intermedia; 1 functional gene) have considerable variability in clinical severity that correlates with the type of mutation and extent of α-globin deficit [36,38,39]. When the disease stems from α-globin gene deletions (termed deletional HbH), anemia is mild to moderate and may require intermittent blood transfusions during periods of stress-induced hemolysis [38,40]. Studies in China, Canada, and California have shown that >50% of patients with HbH disease have deletional mutations [40–42]. When the genotype involves a nondeletional mutation, (termed nondeletional HbH), the disease is often associated with an earlier and more serious phenotype, with profound microcytic anemia with hypochromia (often in utero); low absolute amounts of HbA and HbF; and transfusion dependence and the need for regular iron chelation [38,40–43]. The most common nondeletional HbH genotype is Hb Constant Spring (HbCS; − − / $\alpha^{CS}$ α) due to a mutation in the termination codon of the $\alpha_2$-globin gene that creates an unstable mRNA transcript. Any globin translated from this mRNA is unstable because of translation read-through [44–46].

Recently, scoring systems have been proposed that may help evaluate HbH disease severity and support making treatment decisions in clinical practice [47,48]. In the first, the final validated scoring system comprised age at diagnosis <2 years (score = 1), spleen size ≥3 cm (score = 1) and Hb at steady-state <7 (score = 4) or 7–8 g/dL (score = 3). A cutoff total score ≥ 4 was associated with severe disease that likely requires regular transfusion, with a sensitivity of 89.3% and a specificity of 81.4% [47]. In the second, seven significant criteria (age at thalassemia presentation, age at first blood transfusion, transfusion frequency, growth and development, subcostal spleen size, hemoglobin level, and soluble transferrin receptor level) were each scored 0–2 points to reflect increasing levels of criteria severity. Assigned disease severity categories (mild, 0–5 points; moderate, 6–8 points; and severe, 9–14 points) were validated with 89.47%, 85.15%, and 87.18% consistency, respectively [48].

The most clinically severe type of α-thalassemia is Hb Barts hydrops fetalis syndrome (α-thalassemia major), where no α-globin is produced. When the embryo transforms into the fetus, embryonic hemoglobin production ceases. Since no fetal hemoglobin is made, there is progressive severe anemia, hepatosplenomegaly, and eventually heart failure, leading to Hb Barts hydrops fetalis syndrome and intrauterine fetal death unless intrauterine transfusions are initiated [49]. Newborns with four α-globin deletions/inactivation who retain an intact embryonic ζ-globin gene may produce a small amount of functional Hb Portland ($\zeta_2\gamma_2$), allowing survival into the third trimester without intervention [50].

In more recent years, thalassemia syndromes (including α-thalassemia and β-thalassemia) have been more commonly classified

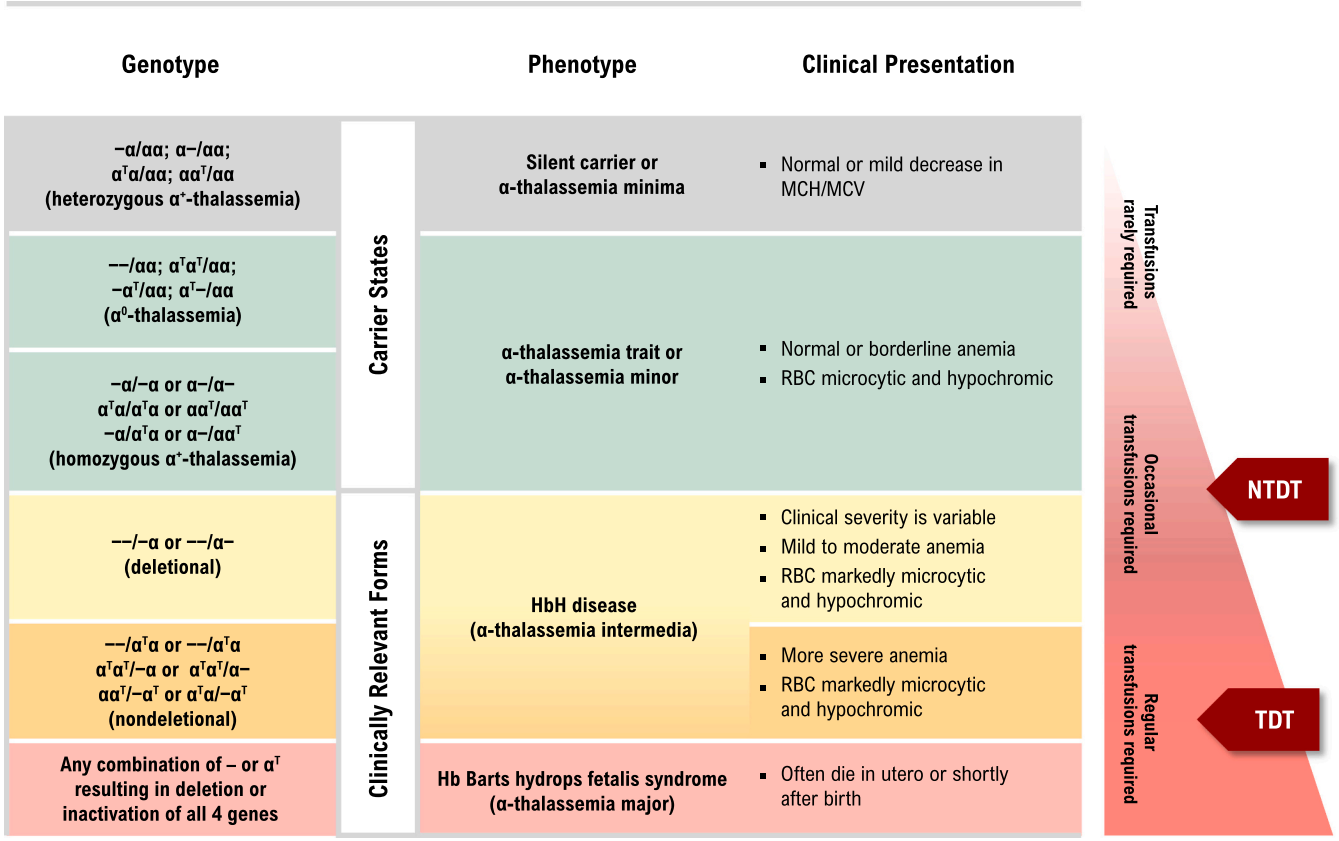


**Fig. 2. Genotype/phenotype correlations and clinical forms in α-thalassemia.** The severity of α-thalassemia widely ranges from heterozygous $\alpha^{+}$-thalassemia with a single gene deletion or inactivation, homozygous $\alpha^{+}$-thalassemia or $\alpha^{0}$-thalassemia with 2 genes deleted or inactivated, deletional HbH disease with 3 genes deleted, nondeletional HbH disease with 2 genes deleted plus 1 nondeletional mutation, up to the most severe form with all 4 genes deleted/inactivated (Hb Barts hydrops fetalis syndrome). Regarding to classification based on transfusion requirement, NTDT encompasses patients who do not require lifelong regular transfusions for survival, although they may require occasional or even frequent transfusions in certain clinical settings for defined periods of time. TDT encompasses patients who require regular blood transfusion to survive; without adequate transfusion support, these patients would suffer several complications and a short life span. *Abbreviations:* Hb, hemoglobin; NTDT, non-transfusion-dependent thalassemia; TDT, transfusion-dependent thalassemia; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; RBC, red blood cells.

phenotypically into two main groups based on the need for regular transfusions: transfusion-dependent thalassemia (TDT) or non-transfusion-dependent thalassemia (NTDT) (Fig. 2) [51–53]. Thalassemia is considered non-transfusion-dependent when patients do not require regular blood transfusions or require them only occasionally or even frequently but for limited periods of time (ie, when certain clinical complications occur). Transfusion-dependent thalassemia refers to patients in whom regular blood transfusions are necessary for survival [52,53]. This classification thus divides the thalassemia population into those with transfusion-related complications (primarily transfusional iron overload) in TDT and those with complications of untreated ineffective erythropoiesis and anemia in NTDT and is now commonly used to define patients' eligibility in clinical trials and to issue separate management guidelines (TDT and NTDT) by the Thalassaemia International Federation (TIF) [52,53]. In the new and upcoming versions of the guidelines, each is further classified into α-thalassemia and β-thalassemia subcategories [54]. It should be further noted that these categories are fluid, and many patients who start as NTDT may transition to become TDT as their transfusion requirement becomes more regular and lifelong [51]. Newer prognostic classification systems are also emerging in β-thalassemia and may become more widely used following prospective validation [55,56].

## 4. Epidemiology

### 4.1. Global picture and role of migration

Historically, α-thalassemia is most prevalent in the Southeast Asian, Mediterranean, Indian subcontinent, Middle Eastern, and African regions [8,26]. Consanguineous marriages account for 20% to >50% of all unions in many communities of North Africa, the Middle East, and West Asia, contributing to a high prevalence in these areas [57–60]. While data are limited for Southeast Asia, a recent systematic review estimated prevalence rates of α-thalassemia (including all deletional/nondeletional mutations) ranging from 17.3% in Malaysia to 51.5% in Vietnam, with an overall prevalence of 22.6% across the Asian countries included for analysis [61]. Surveys have shown carrier frequencies around the Mediterranean ranging from 3% to 4% in Turkey and Italy to 60% in Eastern Saudi Arabia [17]. Almost half of the population in some countries in Africa, such as Nigeria and Kenya, have been observed to carry an α-thalassemia mutation. Parts of India, Papua New Guinea, and Nepal show carrier rates that may be nearing fixation (80% to 90%) [9–11]. According to a recent global systematic literature review, the prevalence of clinically significant forms (HbH disease and Hb Barts hydrops fetalis syndrome) in population-based studies ranged from 0.03/100,000 in Spain for the period 2014–2017 to 4.5/100,000 people in Malaysia for the period 2007–2018. The prevalence in the US ranged from 0.04/100,000 in 2001–2004 (US and Canada) to 0.6/100,000 people in 2004–2008 (US only) [62].

Large-scale global population movements in recent decades have led to increased prevalence of α-thalassemia in many other parts of the world, including northern Europe and the Americas [18,63]. For example, because Asian immigration to the United States has increased over the past few decades, particularly to the West Coast, rates of α-thalassemia have increased [44,64]. A screening study of newborns in California identified HbH disease in approximately 6.7 of 100,000 births (1998–2000) [35]. When infants screened between 1998 and 2006 were included, an α-thalassemia syndrome was identified in 11.1 of 100,000 births; HbH disease was confirmed in the majority of cases (99%) and most occurred in the Southeast Asian population (93%) [65]. As immigrants and a local population intermingle, the carrier and prevalence rates will likely increase, as will incidence rates of clinically relevant forms of α-thalassemia.

The demographic pattern of α-thalassemia also changes with population aging, medical advances, and changes in causes of mortality. Improvement in survival, awareness programs, and screening technologies—as well as decreased pregnancy termination rates from the availability of treatment options—may have contributed to increases in prevalence after the year 2000. On the other hand, increased premarital screening and prenatal thalassemia detection programs have led to a reduction in prevalence in some areas of the world [66–68].

### *4.2. Screening and prevention*

Near the beginning of the millennium, as thalassemia syndromes emerged as a global health burden [2,17,63,69], it was recognized that strategies for screening and prevention of α-thalassemia offer the greatest probability of reducing the number of affected births and deaths [70]. Programs for detecting carriers and informing them of the risk of affected offspring usually lead to a fall in births and deaths of affected children [6]. Other than prenatal testing by amniocentesis or chorionic villus sampling, newborn screening offers the earliest possible recognition and intervention for HbH disease before significant complications, such as life-threatening anemia, hepatosplenomegaly, or bone changes occur. This benefits communities with large proportions of at-risk individuals. Traditionally, newborns were only screened to identify and measure the presence of Hb fractions [71], whereas clinicians today recognize the importance of also determining the child's genotype. While measurement of Hb fractions can inform provisional actions such as referral to a specialist or further laboratory tests, the confirmed genotype is essential to exclude false-positive cases, inform management and appropriate therapy, and provide information to at-risk couples who can then make informed decisions regarding future pregnancies [50,70–73].

According to a study by the Global Globin Network (GGN), six of their member countries—Cyprus, France, Italy, Malaysia, Singapore, and the United Kingdom—have comprehensive screening and prevention programs [70]. These countries have achieved zero or low birth rates of thalassemia despite a high carrier prevalence, freeing funds for the optimized management of existing patients. Prenatal diagnosis and carrier screening are also standard practice in Australia, New Zealand, Northwestern Europe, India, Thailand, many parts of the Middle East, and North America, among others [6,70]. Successful and sustainable screening for α-thalassemia must include follow-up strategies to track patients and enter them into treatment programs. Importantly, follow-up strategies should be managed by primary care physicians and guided by factors that impact the local population, such as disease prevalence, ethnic variation, level of consanguinity, and the local healthcare system [74].

## 5. Pathophysiology

Imbalance in the α/β-globin chains and accumulation of non–α-globin chain tetramers result in apoptosis of maturing nucleated erythroid cells, a state referred to as "ineffective erythropoiesis" [75,76]. Ineffective erythropoiesis may be different in both quality and magnitude between α- and β-thalassemia, leading to varying secondary pathophysiology and morbidity profiles. Generally, hematopoietic expansion follows in an attempt to compensate, both within the bone marrow ("medullary expansion") with damaging effects to neighboring bone and outside the bone marrow in various hematopoietic tissues around the body (leading to hepatosplenomegaly and formation of extramedullary hematopoiesis [EMH] pseudotumors). Red cells that manage to make it to circulation also die prematurely. Collectively, this leads to chronic hemolytic anemia without significant reticulocytosis and an array of secondary pathophysiologic mechanisms, including hypercoagulability and increased intestinal iron absorption leading to primary iron overload [40,53,77,78]. These pathophysiological mechanisms lead to numerous clinical manifestations involving multiple organ systems that need continual monitoring throughout the patient's life (even for milder syndromes) to promptly detect and address emerging complications [4,53].

## 6. Diagnosis

A precise diagnosis of α-thalassemia, with genetic testing to identify genotype, is crucial for reducing the long-term burden of disease. Many individuals with α-thalassemia minima or trait/minor never know they carry an α-thalassemia mutation. If not identified during newborn screening, patients with α-thalassemia minima or trait/minor or mild HbH disease are usually diagnosed after routine blood work or with the development of mild symptoms of anemia. Fetuses with Hb Barts hydrops fetalis syndrome are diagnosed prenatally; this will be described in more detail in a later section (Pregnancy).

### *6.1. Work-up and differential diagnosis of anemia*

As with any patient presenting with anemia, the first assessment should comprise a routine hematological assay with a complete blood count, including red cell indices and a reticulocyte count, and iron studies, including transferrin saturation and a ferritin level (Fig. 3). Red cell parameters alone may not be sufficient to differentiate between anemia due to thalassemia or anemia due to iron deficiency in all cases. While the anemia is microcytic in both, red cell counts are usually normal or high in milder forms of α-thalassemia compared to iron deficiency. Serum ferritin levels will be normal or slightly increased in thalassemia and decreased in iron-deficient anemia; transferrin saturation will be normal or elevated in thalassemia and decreased in iron-deficient anemia [26]. A peripheral smear may also be informative if α-thalassemia is suspected, as HbH can be identified by light microscopy; the β tetramers defining the disease precipitate in circulating erythrocytes, forming HbH inclusion bodies that can be observed with the supravital stain, brilliant cresyl blue [79].

### *6.2. Specialized laboratory tests and genetic testing*

In a differential diagnosis, after ruling out iron deficiency, separation and evaluation of Hb—typically using capillary zone electrophoresis or high-performance liquid chromatography (HPLC)—should follow (Fig. 3) [50]. This will reveal the presence and quantities of various Hb molecules, including HbA, HbH, HbF, and Hb Barts. HPLC analysis should be within seven days of sampling, as normal Hbs may degrade to methemoglobins over time, leading to added peaks that prevent accurate detection of Hb types [26,79]. In patients with 2 or 3 functional α-globin genes, the hemoglobin quantitation may show normal proportions of the different hemoglobins for age, whereas in β-thalassemia, HbA2 and HbF are usually elevated. In individuals with HbH disease, one may detect some HbH and some Hb Barts, or any abnormal hemoglobin formed as a result of a nondeletional mutation.

The only way to clarify ambiguous phenotypes and confirm diagnosis of a specific variant of α-thalassemia is by DNA analysis. Gene sequence

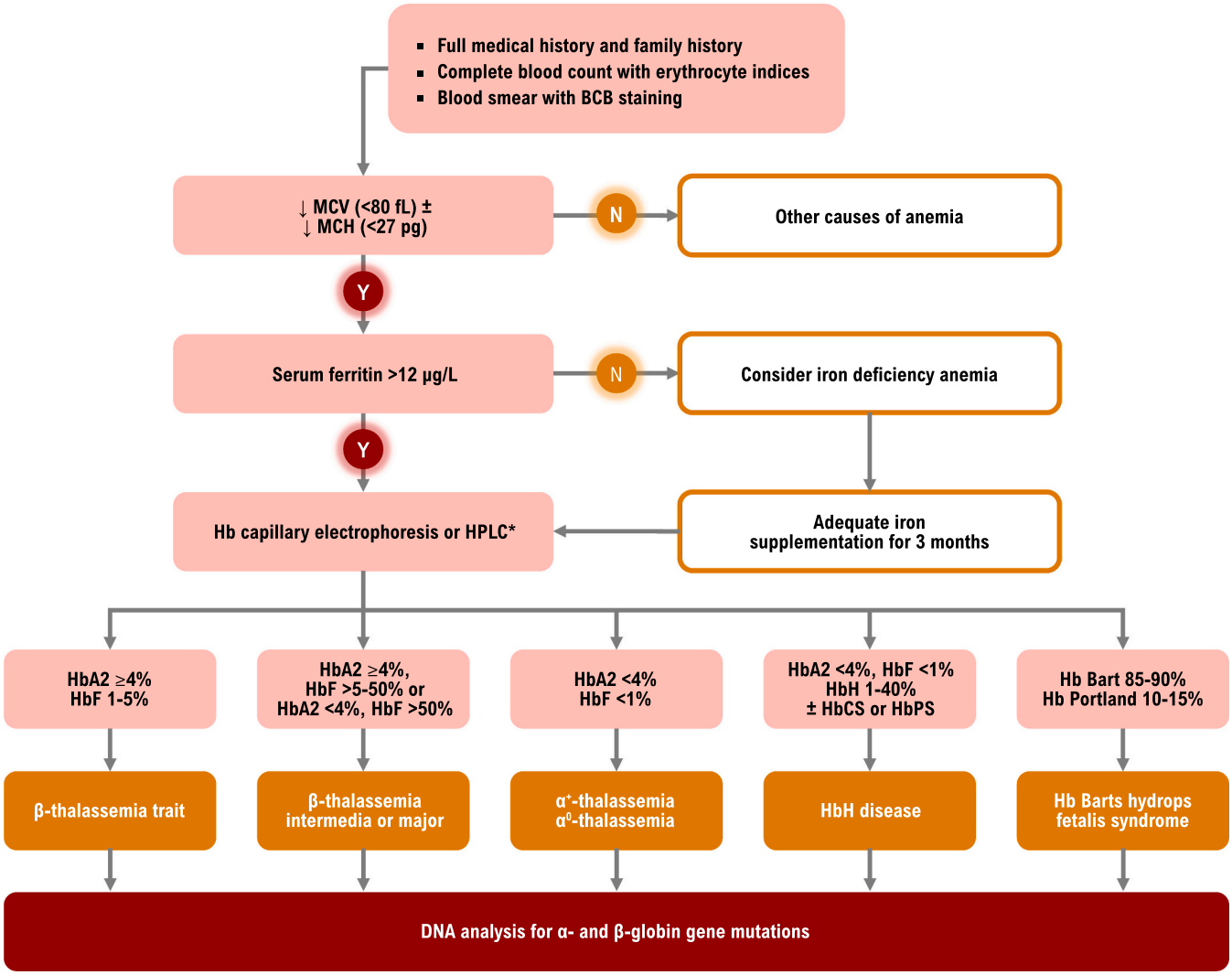


**Fig. 3. Algorithm for screening and diagnosis of α-thalassemia.** *Could also detect co-inherited structural hemoglobin variants indicating HbE, HbS, HbC and other disorders. The presence of HbA2 ≥ 4% does not always exclude α-thalassemia. In individuals of Southeast Asian, Filipino, or Chinese descent who have microcytic hypochromic anemia, an α-globin gene deletion and common variant analysis should be performed, irrespective of HbA2 level. Hb Barts hydrops fetalis syndrome is usually diagnosed prenatally, see Fig. 5. *Abbreviations:* BCB, brilliant cresyl blue; Hb, hemoglobin; HbA2, adult hemoglobin 2; HbCS, hemoglobin Constant Spring; HbF, fetal hemoglobin; HbH, hemoglobin H; HbPS, hemoglobin Paksé; HPLC, high-performance liquid chromatography; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; N, no; Y, yes.

analysis can confirm a diagnosis at the molecular level and find point mutations. Customary clinical techniques include allele-specific PCR, reverse dot-blot hybridization, real-time PCR, multiple ligation probe amplification technology (MLPA), Sanger sequencing, and next-generation sequencing (NGS) [26]. The most appropriate diagnostic approach is determined by the deletions most frequently identified in a specific population. These methods may improve the speed of α-thalassemia diagnosis and reduce costs [27].

## 7. Clinical manifestations and routine monitoring needs

It is essential that clinicians know and understand steps in the diagnosis of α-thalassemia and what referrals for specialized management and/or genetic counseling need to follow. If the primary care provider (PCP) suspects α-thalassemia following the initial differential diagnosis and primary laboratory tests, the patient should be referred to a hematologist with expertise in thalassemia or to a thalassemia center for Hb typing and DNA analysis [53].

Ideally, managing α-thalassemia involves a multispecialty team of PCPs, hematologists, geneticists, nurses, pharmacists, and dietitians. Although patients with more moderate or severe forms of the disease require specialized care, patients with mild HbH disease can usually go without treatment and be monitored by their PCP or pediatrician for any disease progression or complications [53]. The PCP should also collaborate with the specialist team and provide patient support and information. All adults carrying an α-thalassemia mutation should be referred for reproductive counseling.

### 7.1. Clinical profile

In patients receiving transfusion therapy, clinical morbidity is largely driven by secondary iron overload from regular transfusions, which can lead to end-organ damage [52]. Table 1 summarizes monitoring needs for specific complications and clinical conditions in patients with α-thalassemia, in agreement with TIF Guideline recommendations in patients with NTDT and TDT [52,53], the consensus statement from the Thalassemia Clinical Research Network (TCRN) [80], and other expert reviews [77,81,82], although several of these are essentially based on data from patients with β-thalassemia.

As noted, carriers with $\alpha^{+}$-thalassemia or $\alpha^{0}$-thalassemia are mostly

**Table 1**
Monitoring and management of specific morbidities and clinical conditions [52,53,77,81,82].

| Condition | Monitoring | Frequency* | Age (years) | Management† |
|---|---|---|---|---|
| Hemolytic crisis | Infection screening, electrolytes | With clinical suspicion | – | ▪ Restoration of patient's Hb by RBC transfusion<br>▪ Adequate hydration<br>▪ Correction of blood electrolytes<br>▪ Control of body temperature by various means<br>▪ Antibiotics or antivirals |
| Growth and pubertal delay | Weight | Q visit | – | ▪ Per local standards |
| | Standing and sitting height, and bone age in case of delay | Q6–12 mo | <18 | |
| | Tanner staging | Q12 mo | 10–17 | |
| | Routine assessment for infertility, secondary hypogonadism, and impotence | – | ≥18 | |
| Endocrinopathy | Endocrine tests (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) | Q12 mo | ≥10 | ▪ Per local standards |
| Osteoporosis and bone disease | BMD | Q12 mo | ≥10 | ▪ Per local standards<br>▪ Positive experience with bisphosphonates (oral alendronate, intravenous zoledronic acid, neridronate, and pamidronate) in thalassemia but lack supporting data specific to α-thalassemia<br>▪ Encouraging physical activity, discouraging smoking, and ensuring adequate intake of calcium and vitamin D to prevent fractures<br>▪ Adequate management of hypogonadism |
| | Physical exam for bone deformity | Q visit | | ▪ Per local standards |
| Thrombotic events | Thrombotic risk assessment | During admissions, surgery, pregnancy, especially if splenectomized NTDT | ≥18 | ▪ Antiplatelet therapy in splenectomized patients<br>▪ Primary and secondary prophylaxis or treatment with anticoagulant/antiplatelet therapy per local standards |
| Pulmonary hypertension | Echocardiographic assessment of TRV | Q12 mo, especially if splenectomized NTDT | ≥18 | ▪ Per local standards following confirmation by right heart catheterization |
| Heart failure and arrythmias | Echocardiography and ECG | Q12 mo | ≥10 | ▪ Per local standards |
| Liver fibrosis, cirrhosis, HCC | ALT, AST, bilirubin | Q6 mo if NTDT, Q3 mo if TDT | – | ▪ Per local standards |
| | Liver ultrasound | Q12 mo, especially if chronic hepatitis | ≥18 | |
| Gall stones | Laboratory testing and imaging | With clinical suspicion | – | ▪ Per local standards |
| Leg ulcers | Physical examination for skin changes | Q visit, especially if NTDT | | ▪ Per local standards<br>▪ Leg elevation<br>▪ Topical antibiotics, sodium nitrite cream, and occlusive dressing<br>▪ Benefit of pentoxifylline, hyperoxygenation, or transfusion |
| EMH | Physical examination for hepatosplenomegaly | Q visit | – | ▪ Splenectomy for f hypersplenism or symptomatic splenomegaly |
| | Imaging for EMH pseudotumors | With clinical suspicion | – | ▪ Hypertransfusion, radiotherapy, surgery |
| Viral hepatitis and other infections | Serologic testing for hepatitis C and B and HIV | Q12 mo, if TDT | | ▪ Per local standards<br>▪ Vaccination for hepatitis B and A<br>▪ DAA or peginterferon plus ribavirin for hepatitis C |
| Pregnancy | Iron overload, hepatic function, cardiac function, endocrine function, calcium, vitamin D, bone health, infection and alloantibodies screening, thrombotic risk assessment, gall stones assessment | Pre-pregnancy | – | ▪ Iron overload and thyroid function optimization pre-conception<br>▪ Folic acid pre-conception<br>▪ Discontinuation of oral iron chelation for conception and pregnancy and breast feeding (deferoxamine can be used during the 2nd and 3rd trimesters)<br>▪ Appropriate discontinuation and reintroduction of medications used to treat various morbidities<br>▪ Repletion of calcium and vitamin D<br>▪ Appropriate immunizations (hepatitis B, pneumococcal vaccine, influenza)<br>▪ Maintenance of Hb >10 g/dL<br>▪ Prophylactic anticoagulation with aspirin or LMWH for women at high risk (pre- and/or post-partum) |

(*continued on next page*)

**Table 1** (*continued*)

| Condition | Monitoring | Frequency* | Age (years) | Management† |
|---|---|---|---|---|
| | | | | ▪ Avoidance of breast-feeding if positive for hepatitis B or C or HIV |
| | Iron overload, cardiac function, hepatic function, thyroid function, gestational diabetes, ultrasound for growth retardation, prenatal diagnosis | During pregnancy | – | |

*Abbreviations:* ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMD, bone mineral density; DAA, direct-acting antiviral drug; ECG, electrocardiogram; EMH, extramedullary hematopoiesis; Hb, hemoglobin; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; LMWH, low-molecular-weight heparin; mo, months; NTDT, non-transfusion-dependent thalassemia; RBC, red blood cell; TDT, transfusion-dependent thalassemia; TRV, tricuspid-valve regurgitant jet velocity; Q, every.

* Closer monitoring may be needed in case of abnormality, while longer intervals may be considered in patients with no abnormality for several assessments. Additional diagnostic tests may be needed to confirm diagnosis.

† Adequate management of anemia and iron overload are necessary to prevent/manage all conditions. Management to include prompt referral and consultations with relevant specialists.

asymptomatic, and have no complications related to their mild anemia. Such individuals may be followed by their primary providers with referral to a hematologist when needed. They should be referred for genetic counseling when of childbearing age. Rarely, with a severe stressor, their Hb level may drop and they may need an episodic transfusion, but this is extremely uncommon. If there is a significant drop in Hb level in an α carrier, the presence of another hematological disorder should be explored.

Most patients with deletional HbH disease do not become transfusion dependent, and some never seek medical consultation [39,45,83,84]. However, an analysis of US commercial and government insurance claims databases between 2013 and 2021 evaluated the clinical burden of patients with α-thalassemia and β-thalassemia compared with matched controls with no history of thalassemia or hemolytic anemia (patients matched on age, sex, follow-up period, and payer type) [85]. Patients with NTD α-thalassemia were more likely to have cardiovascular disease (7.2% vs 4.7%; $p < 0.001$), osteoporosis (3.9% vs 2.6%; $p < 0.005$), cerebrovascular disease (3.8% vs 1.9%; $p < 0.001$), hypogonadism (1.8% vs 1.0%; $p = 0.005$), pulmonary hypertension (1.1% vs 0.3%; $p < 0.001$), jaundice (1.0% vs 0.2%; $p < 0.001$), and liver disease (1.2% vs 0.4%; $p < 0.001$) compared with matched controls. Overall mean (SD) comorbidities were also higher in patients with NTD α-thalassemia compared with matched controls (1.7 [1.5] vs 1.1 [1.2]; $p < 0.001$) [85].

Clinical and hematological manifestations in patients with a non-deletional genotype are more severe vs those with deletional HbH disease and can be remarkedly variable [39,83]. Comparison of clinical characteristics between patients with nondeletional and deletional HbH disease shows that patients with nondeletional HbH disease are more often transfusion-dependent (20% to 30% vs rare), with higher risk of impaired growth and bone changes (15% to 20% vs rare), splenomegaly (with/without hypersplenism; 20% to 30% vs 10% to 20%), and gallstones (20% to 30% vs 10%) [45,86]. Clinical features of Hb Barts hydrops fetalis syndrome are intrauterine anemia, edema, hepatosplenomegaly, skeletal deformities, retardation in brain growth, and cardiovascular deformities and failure [38]. Hb Barts hydrops fetalis syndrome will be further discussed in a later section (Pregnancy).

### 7.2. Chronic anemia

Heterozygous $\alpha^{+}$-thalassemia usually generates enough α-chains to ensure normal Hb synthesis [26]; these patients present with no or very slight anemia. However, mild anemia usually occurs in patients with homozygous α + −thalassemia or $\alpha^{0}$-thalassemia (Hb <13.5 g/dL [males] or < 12.0 g/dL [females]). Although all patients with HbH disease present with anemia, extent can vary (Hb 4–13 g/dL), even among patients with the same genotype [52,86]. In general, as compared to deletional HbH disease, those with nondeletional HbH disease generally have more severe anemia. An analysis of 106 patients with deletional HbH disease and 46 with nondeletional HbH disease enrolled in the TCRN showed that non-transfused anemia was more severe in patients with nondeletional HbH disease (mean [SD] Hb 9.4 [0.8] g/dL vs 8.7 [1.5] g/dL, respectively) [87].

A conservative approach to managing anemia is now in question. Emerging evidence from patients with NTD β-thalassemia shows that Hb levels <10 g/dL are associated with a greater risk of long-term morbidity and mortality, and such risk can be mitigated by increases of 1 g/dL [88]. This prompted a call for treating anemia in this patient population and challenged earlier beliefs that mild to moderate anemia can go untreated in NTDT [89]. Consequently, a baseline Hb concentration of ≤10.0 g/dL is frequently included as an eligibility criterion in clinical trials of novel agents for NTDT [90]. Ineffective (inadequate) transfusions in TD β-thalassemia patients has also been associated with shortened survival, as observed in studies in resource-limited countries [91]. However, it is important to keep in mind that unlike in β-thalassemia, the degree of ineffective erythropoiesis is much lower in α-thalassemia, and such individuals may not need intervention as they will likely not have the same complications as those with β-thalassemia.

### 7.3. Iron overload

The human body has limited ability to excrete excess iron [92]. Primary iron overload arises from ineffective erythropoiesis signals that increase intestinal iron absorption through low hepcidin levels; while secondary iron overload arises from recurrent transfusions [52,53,75,76,93,94]. Historically, ~70% to 75% of individuals with HbH disease will develop some degree of iron overload by adulthood, regardless of transfusion history [95–98]. Children with HbH disease do not appear to develop iron overload at the same rate as adults, because more iron is needed for growth [40]. A longitudinal study of 86 cases of HbH disease (median follow-up 2.6 years [range 0.1–14.6 years]) showed that serum ferritin levels did not increase significantly between birth and 18 years ($p = 0.12$); patients aged >18 years showed a strong positive correlation between ferritin level and age ($p < 0.001$) [40].

The dynamics of primary (NTDT) and secondary (TDT) iron overload are different. Studies from patients with β-thalassemia have shown that primary iron overload has preferential iron storage in the liver leading to elevated liver iron concentration (LIC), while the heart is spared. Similar observations have also been made in small studies with HbH disease [99]. Primary iron overload is also associated with increased release of iron from the reticuloendothelial system, leading to inappropriately low serum ferritin levels (levels in NTDT being lower than expected for the same LIC compared with patients with TDT) [100]. In secondary iron overload, saturation of transferrin leads to the formation of non–transferrin-bound iron species which can readily enter all body organs and cause damage, especially to the heart, liver, and endocrine glands [52,53,100,101].

Early identification of iron overload is important for adults with HbH

disease as prompt management can prevent serious clinical morbidities. In patients with β-thalassemia, iron chelation therapy is usually considered after 10 to 12 transfusions in TDT, with LIC and cardiac T2* (measure of myocardial iron concentration) values >15 mg/g and < 20 ms, respectively, indicating increased risk of morbidity and mortality [52,100,102–105]. Lower thresholds of serum ferritin >800 μg/L (and corresponding LIC >5 mg/g) have been associated with increased hepatic, endocrine, and vascular morbidity and with increased mortality in NTD β-thalassemia and are used to flag the need for iron chelation therapy [106–109]. Similar associations between elevated serum ferritin and LIC and hepatic disease have also been observed in patients with HbH disease [97,110], though the prevalence of iron overload in NTD α-thalassemia is likely much lower than in NTD β-thalassemia because of the lower degree of ineffective erythropoiesis.

Evaluating serial serum ferritin levels is the easiest and most widely available way to assess iron overload; however, results may be affected by factors beyond body iron stores, such as hemolysis, ascorbate deficiency, inflammation, and liver disease [111]. When available, assessment of LIC and cardiac T* by noninvasive MRI techniques can provide valuable information on hepatic and cardiac iron overload and are strongly recommended to allow tailoring of iron chelation therapy. Recommendations for the monitoring (and management, see later section [Iron Chelation]) of iron overload in patients with HbH disease are summarized in Fig. 4.

### 7.4. Specific morbidities

Several complications linked to chronic anemia and ineffective erythropoiesis include hyperhemolysis, endocrinopathies (especially diabetes mellitus) and bone disease, cardiovascular disease, chronic leg ulcers, liver complications, gallstones, and EMH.

#### 7.4.1. Hyperhemolysis

Although most patients with HbH disease remain clinically healthy without regular transfusions, sporadic episodes of hyperhemolysis requiring RBC transfusions may occur. Hyperhemolysis leading to severe anemia may be triggered by acute infection and high fever, or other stressors such as surgery [45]. Hb levels may rapidly drop to as low as ≤3 g/dL [112], accompanied by hemoglobinemia and hemoglobinuria (intravascular hemolysis) and resulting in renal damage and insufficiency, and ultimately acute renal failure [53]. Patients must therefore be continually monitored, especially during acute infections and pyrexia, oxidative stress, hypersplenism, or pregnancy [50].

#### 7.4.2. Endocrinopathies and bone disease

The medullary expansion that follows from ineffective erythropoiesis leads to many of the bone complications observed in children and adults with thalassemia, including bone deformities and osteoporosis [75,76,113]. In addition, an association between iron overload and growth retardation, delayed sexual development, and endocrinopathies has been well established in patients with TD β-thalassemia [113–116]. A study of 361 TCRN patients with any thalassemia syndrome showed

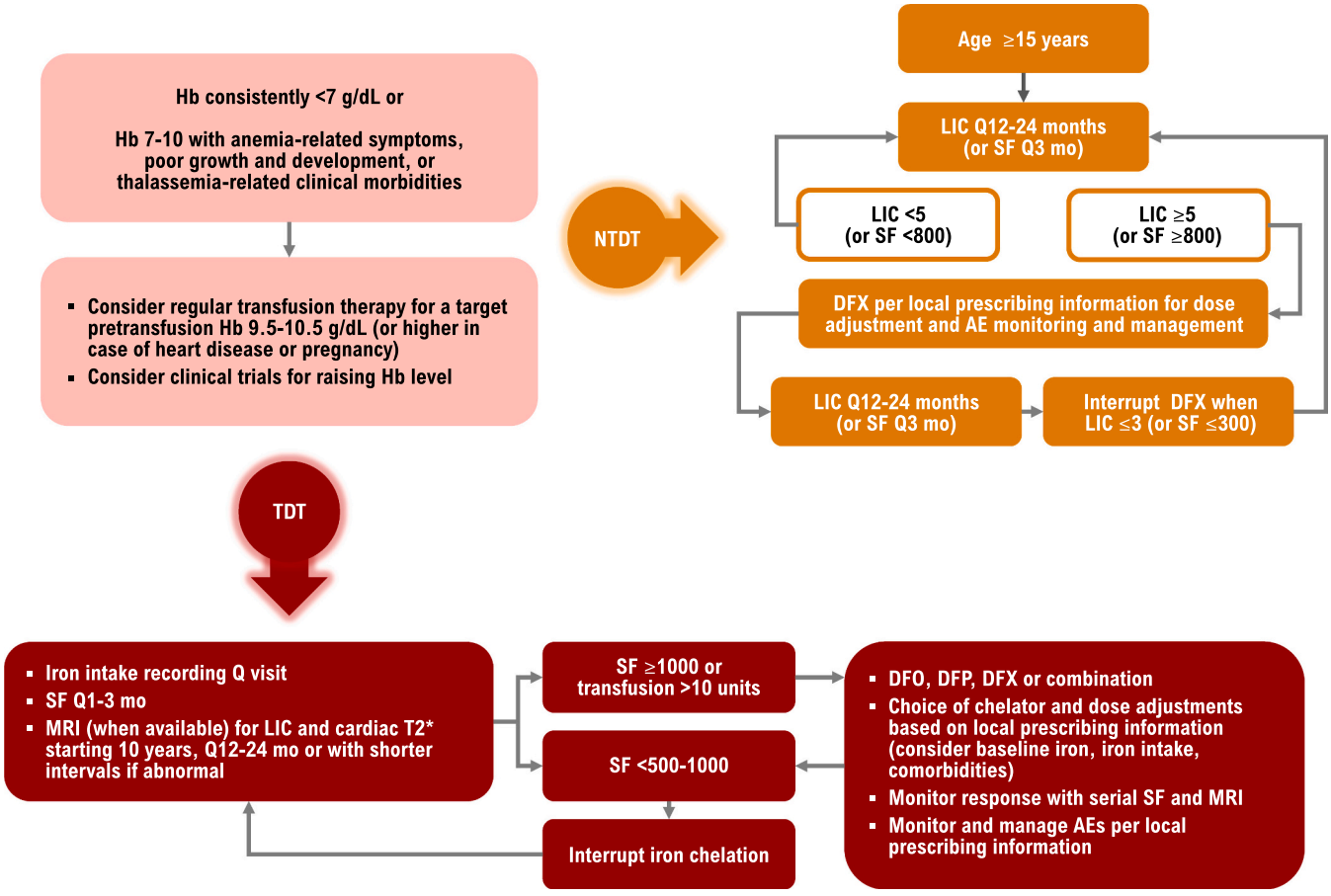


**Fig. 4. Monitoring and management of anemia and iron overload in hemoglobin H disease.** Common adverse events for iron chelators include: DFO, ocular and auditory symptoms, bone-growth retardation, local reactions, and allergy; DFP, gastrointestinal symptoms, arthralgia, agranulocytosis, and neutropenia; DFX, gastrointestinal symptoms, increased creatinine levels, and increased hepatic enzyme levels. Adherence should be regularly monitored in all patients on iron chelation. *Abbreviations:* AEs, adverse events; DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox; Hb, hemoglobin; LIC, liver iron concentration in mg/g; mo, months; SF, serum ferritin in μg/L; Q, every.

that 60% to 75% of adult patients showed reduced bone mass for their age [117]. In addition, many patients aged 20 to 30 years who may not yet have attained peak bone mass, had early onset of osteopenia and osteoporosis, especially those dependent on transfusions. Estimated mean (95% confidence interval) spine bone mineral density (BMD) *Z*-scores of a 20 year old with deletional and nondeletional HbH disease were − 1.64 (−2.16,−1.11) and − 2.00 (−2.52,−1.49), respectively, indicating suboptimal peak bone mass [117]. High osteoporosis rates were also observed in a single-center, prospective study of patients with NTDT in Thailand (26.3%) [110].

Once again, most of the data are from patients with β-thalassemia and data specific to α-thalassemia are relatively sparse. An analysis in Guangxi Province, China of 200 children with HbH disease (deletional and nondeletional) aged 3 to 12 years showed that 68.5% of patients had growth retardation, 84.0% hypogonadism, 14.5% hypoparathyroidism, 13% hypothyroidism, and 7% diabetes mellitus, all significantly more prevalent compared with age-matched normal controls ($p \leq 0.001$) [118]. A prospective study in Thailand of 57 adult patients with NTDT aged 18 to 74 years (59.6% β-thalassemia and 40.4% HbH disease) showed that in patients with HbH disease ($n = 23$), 13.0% had osteoporosis, 4.3% hypogonadism, and 4.3% diabetes mellitus [110]. In Thailand, 40 children, adolescents, and young adults aged 10 to 25 years with HbH disease (nondeletional $n = 17$; deletional n = 23) were followed for 2 years [119]. There was a high prevalence of patients (52.5%) with an abnormal insulinogenic index, which indicated abnormal early-phase insulin secretion from β-cells, with no significant difference between nondeletional and deletional HbH disease.

#### 7.4.3. Cardiovascular disease

Cardiomyopathy and arrhythmias are the main consequences of cardiac iron overload in patients with TDT, especially those reaching serum ferritin values >2500 μg/L and cardiac T2* values <20 ms [103,120]. Although cardiac disease has historically been the most common cause of death in patients with TD β-thalassemia, advances in iron overload monitoring and chelation have ensured this is no longer the case [121–123]. Cardiovascular disease, not necessarily iron-mediated, is also the leading cause of death in NTD β-thalassemia patients [124].

A hypercoagulable state has also been established in patients with thalassemia and attributed to thrombogenic potential of hemolyzed RBCs, platelet activation, and other disturbances in coagulation [125]. Data from patients with β-thalassemia indicate that thrombotic disease, mostly venous, affects ≈14% of the patient population [126]. The risk for thrombotic events is highest in splenectomized adults with NTDT, considering the 'wash-out' and scavenging roles of transfusions and the spleen for hemolyzed RBCs and activated platelets [126–129]. Such patients should always be considered as high risk for thrombosis in medical and surgical risk assessment models [130]. Pulmonary hypertension is also common in splenectomized adults with NTDT (data from β-thalassemia indicating prevalence up to 11% suggested by echocardiography parameters and up to 5% confirmed by cardiac catheterization) and can lead to substantial mortality [131,132].

A study was conducted in 91 patients with thalassemia in northern Thailand to evaluate the prevalence of cardiac iron overload and cardiovascular complications (19% HbH disease; 46% TDT; 84% receiving iron chelation) [133]. Cardiac iron overload (cardiac T2* <20 ms) was found in 10 patients (11%), and 21 patients (23%) had cardiovascular complications; 7 (8%) had cardiomyopathy (all TDT) and 14 (15%) had pulmonary hypertension (8 NTDT and 6 TDT) [133]. Other studies have also revealed pulmonary hypertension prevalence rates in patients with HbH ranging from 6.5% to 15.8% (by echocardiography) with a clear association with advancing age but not splenectomy [110,134].

#### 7.4.4. Liver complications

Iron overload and viral hepatitis are the main causes of liver complications (ie, chronic inflammation, fibrosis, and cirrhosis) in patients with thalassemia [52,53,97,110]. Moreover, hepatitis B or C are independent risk factors, which together with iron overload can hasten progression, even leading to the development of hepatocellular carcinoma [52]. Liver disease is recently regarded as a major cause of mortality in both NTDT and TDT patients, especially those not receiving adequate iron chelation therapy [122–124].

#### 7.4.5. Gallstones

Approximately 38% to 52% of patients with HbH disease have "silent gallstones" [45,110]. These patients may develop acute and/or chronic cholecystitis (with or without known gallstones), which is very difficult to diagnose based on clinical symptoms alone. Gallstone formation is a factor of the degree of anemia and hemolysis [110]. Patients with thalassemia (including those with HbH disease) who present with "peptic ulcer–like" symptoms should be referred for ultrasonography if symptoms do not dissipate with treatment [52,135]. Patients with HbH disease who are homozygotes or double heterozygotes for Gilbert alleles have a significantly increased risk of gallstones and jaundice [136].

#### 7.4.6. Leg ulcers

Leg ulcers are a painful and indolent complication of NTDT [137], which are attributed to chronic hypoxia, local iron overload deposits, and hypercoagulability-related ischemia; they may increase disability and disrupt quality of life [53].

#### 7.4.7. Extramedullary hematopoiesis

Extramedullary hematopoiesis is common in patients with thalassemia not requiring regular transfusions (NTDT]) [76,138]. It is thought that >80% of EMH cases may remain asymptomatic, with pseudotumors discovered only incidentally by radiologic techniques [53]. A 3-year case-control study showed that of 17 patients with HbH disease enrolled and screened by computed tomography or MRI, 47% had EMH pseudotumors [139]. In other observational studies, prevalence rates were lower than those reported in β-thalassemia and ranged between 0 and 8% [110,140,141]. Although different anatomical locations may be involved, paraspinal involvement is most concerning due to potentially debilitating permanent clinical consequences secondary to spinal cord compression [139]. EMH in the spleen and liver can lead to hepatosplenomegaly [53], which is more common in nondeletional HbH disease [142].

### 7.5. Prognosis and mortality

Persons with $\alpha^{+}$-thalassemia or $\alpha^{0}$-thalassemia usually have the same life expectancy as the general population [28,143]. While some patients with HbH disease may lead normal lives, the prognosis for many is varied and dependent on the severity of the morbidities associated with their disease.

Symptomatically severe HbH disease (particularly nondeletional HbH) has historically been life threatening, often resulting in fetal, newborn, or adolescent death [144–146]. However, with improved availability of safe and effective blood transfusions and iron chelation therapies, the development of evidence-based standardized protocols for the management of anemia and iron overload, greater awareness and care of α-thalassemia complications, and the implementation of multidisciplinary care, patients are surviving for longer periods with improved quality of life [52,53,111].

Infants with Hb Barts hydrops fetalis syndrome have historically either died in utero (at 23–38 weeks) or shortly after birth [147–151]. While intrauterine transfusions (IUTs) and intrauterine exchange transfusions (IUETs) enabled affected fetuses to survive the perinatal period [150,152], the family and healthcare providers may face ethical challenges. Such individuals would be transfusion dependent if they survived, with all of the attendant complications.

### 7.6. Quality of life

While the health-related quality of life (HRQoL) burden of β-thalassemia is well documented, data in α-thalassemia are limited. A single study on HRQoL in pediatric patients (aged 2 to <18 years) in Thailand with transfusion-dependent HbH disease ($n = 5$) and β-thalassemia ($n = 44$) found that Pediatric Quality of Life Inventory total score and psychological, emotional, social, and school functioning subdomain scores were similar between HbH and β-thalassemia patients [153]. Quality comprehensive healthcare and adherence to internationally accepted evidence-based guidelines have resulted in improved quality of life for patients with HbH disease, especially in economically developed countries. Early and regular monitoring allows for early recognition and treatment of complications, and would thus, improve outcomes in terms of survival and quality of life [52,53,80,146,154].

### 7.7. Economic burden

Hemoglobinopathies are recognized as a health burden in 71% of 229 countries worldwide that together account for 89% of all global births [6,70]. In 1 US study, adults and children with nondeletional HbH disease had 1.7 times more annual clinic visits and 3.9 times more hospital admissions compared with patients with deletional HbH disease ($p < 0.001$ for both) [40]. A retrospective, prevalence-based, cost-of-illness analysis of the United Arab Emirates (UAE) healthcare system showed that patients with α-thalassemia intermedia had a significantly higher median number of laboratory tests than those with other thalassemia subtypes (β-thalassemia major, β-thalassemia intermedia, and HbE/β-thalassemia) ($p = 0.035$) [155].

While information regarding the global economic burden of α-thalassemia is sparse [156], it is known that a great portion of the health burden is borne by countries with inadequate resources for healthcare. This burden will only grow as more patients with the disease survive and live longer lives and the need for long-term treatment increases. As an example, donor blood for transfusion, already of limited supply, will require screening for hepatitis B and C, human immunodeficiency virus, and, in many countries, malarial parasites. Facilities for screening for and treating thalassemias and training programs for medical staff will need to be further developed, in both high-frequency regions and in richer, industrialized countries where prevalence is increasing due to immigration, such as Northwestern Europe and North America. There is also an urgent need to determine projected costs for meeting these healthcare burdens accurately and realistically, so that allocation of resources and the most economic and effective approaches can be planned [6,69,70].

## 8. Clinical management

### 8.1. General principles

While patients with $\alpha^{+}$-thalassemia or $\alpha^{0}$-thalassemia normally do not need specific treatment unless they are anemic, some principles about general management can be applied for all patients with α-thalassemia. Although evidence in α-thalassemia is limited, in general, patients should receive supplementary folic acid (up to 5 mg/day), multivitamins including vitamin D and an antioxidant (ie, vitamin E 10 U/kg/day), and nutritional supplements (ie, calcium and zinc) to support increased bone marrow activity (erythropoiesis) and offset increased oxidative stress [38,86,157]. Care should be taken to ensure that these supplements do not contain iron, which would be absorbed more rapidly and could lead to primary iron overload more rapidly.

### 8.2. Transfusion therapy

Regular transfusion is the mainstay of therapy in patients presenting with severe anemia (Hb <7 g/dL) and symptoms, such as those with nondeletional HbH disease or Hb Barts hydrops fetalis syndrome. In patients with less severe anemia (Hb 7–10 g/dL), there is mounting evidence from β-thalassemia studies of increased morbidity and mortality and the need for intervention [89]. Observational studies also confirm decreased morbidity and mortality in those patients placed on transfusion programs [124,126]. However, the decision to start patients on regular transfusion programs is not easy, considering the added burden of chronic therapy, increased morbidity from secondary iron overload, and healthcare resource utilization [158,159]. The decision to initiate a long-term, regular transfusion regimen should always be taken with caution since many patients are often given transfusions to manage an intercurrent infection or during pregnancy, and they end up remaining on such transfusions indefinitely.

A large proportion of patients with nondeletional HbH disease are transfusion-dependent. In a California study of HbH patients, the likelihood of patients with deletional mutations receiving a transfusion by 20 years of age was 2.8% [40]. By contrast, for patients with nondeletion mutations, this likelihood was 13% by 1 year of age, 39% by 5 years of age, 75% by 10 years of age, and 80% by 20 years of age. The youngest patient in this study to require a transfusion was aged 3 months and had a Hb level of 6.0 g/dL.

Recommendations for the management of anemia and considerations for regular transfusion therapy in patients with HbH disease are summarized in Fig. 4 [52,53]. When transfusions are given patients should receive appropriate vaccinations along with screening of donor and recipient. The risk of alloimmunization is highest in pregnant women, splenectomized patients, and those who have not previously been transfused [52,53]. When a pregnancy has been diagnosed as having a hydropic fetus (Hb Barts), intrauterine transfusions may be initiated to maintain viability until delivery, and then must be continued just as in a TDT patient.

### 8.3. Splenectomy

Many patients with thalassemia develop splenomegaly due to increased destruction of RBC by the reticuloendothelial system, in particular the spleen, together with increased EMH activity [75]. Historically, the rationale for splenectomy in patients with thalassemia was to increase Hb level or decrease blood consumption [52]. All current guidelines for patients with TDT or NTDT recommend a cautious approach and restrict splenectomy only to certain circumstances (ie, hypersplenism and symptomatic splenomegaly) [52,53] due to an increased risk of venous thrombosis and pulmonary hypertension and increased infections after splenectomy [160,161].

### 8.4. Erythroid stimulating agents (ESAs)

The use of recombinant human erythropoietin (ie, epoetin alfa or darbepoetin alfa [DAR]) as erythroid stimulating agents may be associated with increases in total Hb levels in patients with NTDT. Increases in total Hb >2 g/dL have been observed in patients with deletional HbH disease receiving epoetin alfa [162]. However, in a study to assess the response to dose escalation of DAR in patients with thalassemia, the one patient with nondeletional HbH disease had a modest response to DAR, suggesting that DAR stimulation of erythropoiesis may be insufficient to compensate for the higher rate of hemolysis [163]. It bears keeping in mind that this erythroid proliferation without appropriate maturation, which is the hallmark of thalassemia, may lead to worsening marrow expansion, bone pain, and EMH. Hence, these agents are not used much in the thalassemias.

### 8.5. Iron chelation

There are 3 iron chelators differing in binding properties, routes of absorption, metabolism, and elimination that are presently available for TDT patients: deferoxamine (DFO; approved worldwide for first-line

treatment of transfusional iron overload in patients with chronic anemia), deferasirox (DFX; approved as first-line monotherapy for transfusional iron overload in >100 countries worldwide and in the US as treatment of chronic iron overload due to blood transfusions in patients ≥2 years of age), and deferiprone (DFP; approved in the US as first-line treatment of transfusional iron overload in patients ≥3 years of age (oral solution) and patients ≥8 years of age (tablets) with thalassemia syndromes (including α-thalassemia), sickle cell disease, or other anemias and in Europe as treatment of transfusional iron overload in patients with β-thalassemia major when current chelation therapy is contraindicated or inadequate) [52,164–171]. All three iron chelators have adequate efficacy to control systemic, hepatic, and cardiac iron overload, although high doses or combination therapy may be needed in some patients with severe iron overload.

Iron chelation is now recommended in NTDT patients with serum ferritin >800 μg/L or LIC >5 mg/g considering iron-related morbidity and mortality above these thresholds (starting age of 10 years, or higher in HbH disease) [53]. In a small study of 17 patients with HbH disease who were not transfusion dependent, treatment with DFP significantly decreased serum ferritin levels after 6 months and 18 months of treatment, and this decrease was maintained until 24 months [172]. The first study to investigate a chelating agent in a large cohort of patients with NTDT was the THALASSA (Assessment of Exjade in NonTransfusion-Dependent Thalassemia) trial (2008–2011; reported in 2012). In this phase 2, prospective, randomized, double-blind, placebo-controlled trial, the efficacy and safety of DFX were evaluated in 166 patients ≥10 years of age with NTDT and iron overload, including 22 patients with α-thalassemia. At 1 year, both LIC and serum ferritin levels decreased significantly with DFX treatment compared with placebo, with reductions notably seen in α-thalassemia patients receiving dispersible tablet doses as low 5 mg/kg/day [173]. The frequency of adverse events (AEs) in patients receiving DFX was similar to placebo. The most common drug-related AEs were nausea (6.6%), rash (4.8%), and diarrhea (3.6%). The study also included a preplanned, 1-year, open-label extension phase [174]. Here, LIC continued to decrease, and almost 40% of patients achieved LIC <5 mg Fe/g dry weight. The safety profile of DFX was consistent with that in the core study. Further analysis of THALASSA data observed that the efficacy of DFX was dose dependent and consistent across patient subgroups, including those with α-thalassemia [175]. Subsequently, the open-label, single-arm THETIS study supported the efficacy and safety results of the THALASSA trial for up to 5 years of therapy [176]. Based on these data, DFX was approved by the US FDA for treatment of chronic iron overload in patients ≥10 years of age with NTDT syndromes (including α-thalassemia) [177].

Poor adherence to iron chelation, even with oral agents, remains the biggest challenge in practical patient management [52]. Adverse events require close monitoring per local prescribing information but are usually self-limiting and mitigated with appropriate monitoring and dose modifications. Recommendations for the monitoring and management of iron overload in patients with HbH disease are summarized in Fig. 4.

### 8.6. Hematopoietic stem cell transplantation

Until recently, hematopoietic stem cell transplantation (HSCT) was the only curative therapy for thalassemia, as it leads to the replacement of the entire hematopoietic system [178]. While the majority of data are from patients with β-thalassemia, advancements in conditioning regimens, prevention of graft-vs-host-disease, and more effective treatments against infections have improved outcomes to the point where up to 90% of patients with thalassemia who undergo HSCT are cured [52,179–183]. It is recommended that if a human leukocyte antigen (HLA) matched sibling is available, HSCT should be offered to transfusion-dependent HbH and Hb Barts hydrops fetalis syndrome patients at an early age (≤6 years) before complications due to iron overload have developed, as HSCT is cost effective when compared to lifelong supportive therapy and care [52].

Between 1998 and 2021, 15 individual cases of HSCT in patients with Hb Barts hydrops fetalis syndrome, aged 5 months to 13 years, were publicly reported [151,184–194]. The treatment was successful in 13 of those patients, who displayed either mild or no developmental delays. The safety of HSCT in utero is being examined in ongoing clinical trials (NCT02986698, NCT05797272). Successful cases of HSCT in severe HbH disease have also been reported [195].

### 8.7. Management of specific morbidities

Management approaches for specific morbidities and clinical conditions are summarized in Table 1 [52,53,77,81,82]. Thalassemia management requires a multidisciplinary team of specialists who are well-educated about the various manifestations of the disease. Transition of care from pediatric to adult facilities should also be orchestrated through transition programs that take into consideration the various clinical, logistical, and psychological challenges of transition [196]. Management of patients in dedicated expert centers has been associated with improved survival [197].

### 8.8. Well-being and psychosocial care

HbH disease is a chronic disease and as such has a substantial impact on patients and their families. Psychological therapy to help patients cope with complications of the disease and its treatments and achieve a better quality of life is appropriate. Beyond patient education about α-thalassemia, transfusions, and iron chelation, approaches for holistic management of the disease may include cognitive therapy, behavioral therapy, and psychodynamic psychotherapy [198]. If effective, patients may show improvements in mood, coping strategies, and even medical outcomes and adherence to treatment. However, more research is needed in identifying the most important components of psychological intervention among different formats [198].

## 9. Pregnancy

### 9.1. Premarital/conception counseling

When ethically possible, preventing the conception of babies with HbH disease or Hb Barts hydrops fetalis syndrome could include comprehensive prenatal screening and education and counseling of patients at risk (Fig. 5). Genetic screening of a patient's partner or family members to determine if they are carriers of α-thalassemia is recommended when a patient of reproductive age is diagnosed with $\alpha^0$-thalassemia or HbH disease or is a member of an ethnic group at risk. Couples at risk of having a child with Hb Barts hydrops fetalis syndrome should be counseled regarding the risks to the fetus and the pregnancy and the options during pregnancy, including termination, in utero transfusions, and HSCT.

### 9.2. Diagnosis of Hb barts hydrops fetalis syndrome in pregnancy

Couples who are at high risk should be informed of the possibility of in vitro fertilization with preimplantation genetic diagnosis (PGD) of embryos [27,199]. PGD is usually done on blastomeres biopsied from 8-cell stage embryos. Unaffected embryos are then implanted. If pregnancy is successful and religious and ethical issues do not preclude its use, prenatal genetic diagnosis (PND) is performed at approximately 11 weeks gestation to confirm PGD results [199].

Prenatal diagnosis of Hb Barts hydrops fetalis syndrome in spontaneous pregnancies in affected couples can be made by globin gene analysis using chorionic villus sampling (10–14 weeks gestation), amniocentesis (after 15 weeks gestation), or fetal blood sampling (18 weeks gestation) [184,200,201]. Fetal abnormalities predictive of Hb Barts hydrops fetalis syndrome that can be detected by the second trimester using ultrasound include general edema, ascites,

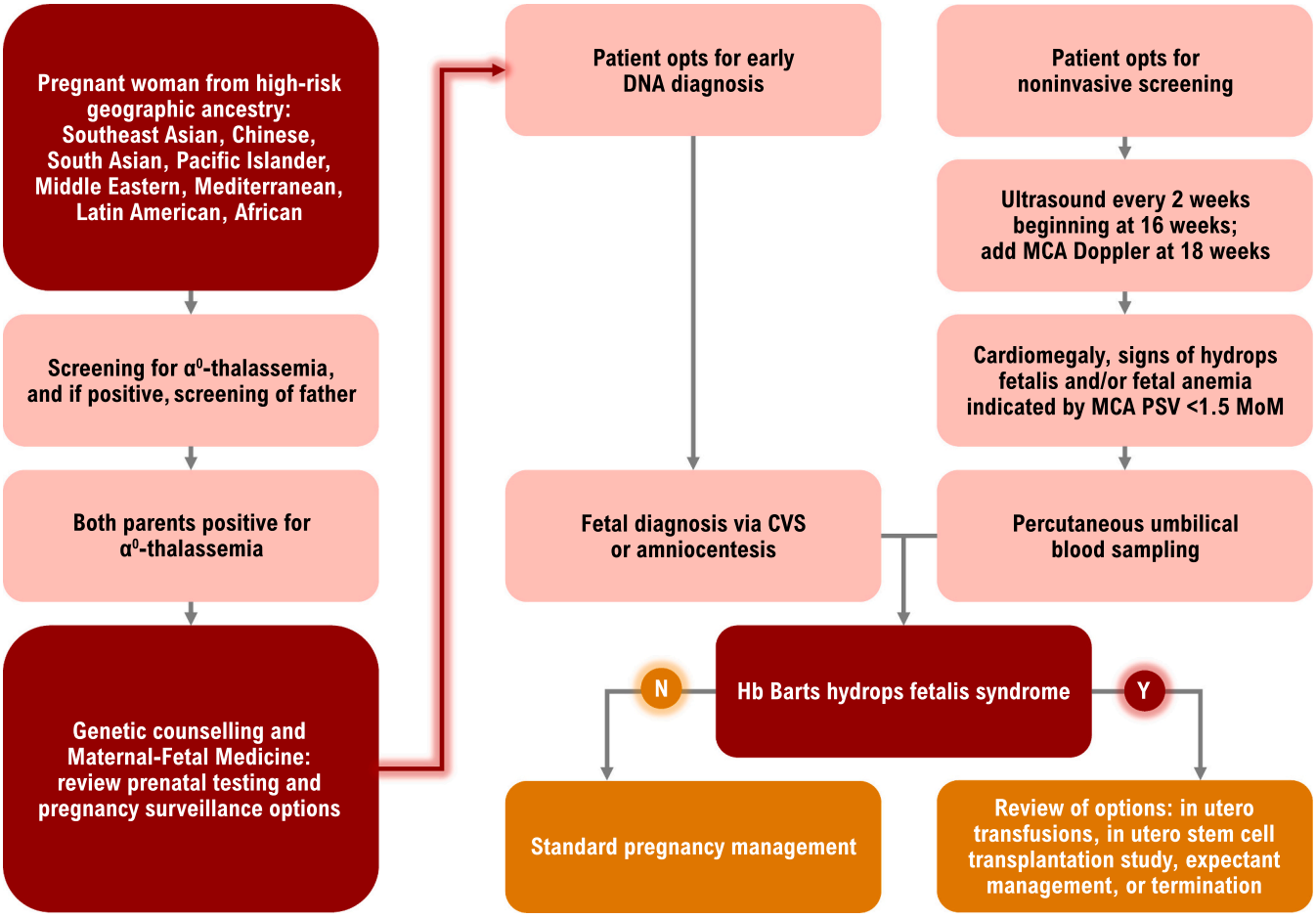


**Fig. 5. Prenatal screening for Hb Barts hydrops fetalis syndrome.** It is recommended that all pregnant women have a CBC with assessment of MCV at first clinical visit. In high-risk cases, or where Hb electrophoresis is abnormal, consultation with a genetic counselor and/or hematologist is recommended. Please note: genetic counseling may happen at any time in this pathway. *Abbreviations:* CBC, complete blood count; CVS, chorionic villus sampling; Hb, hemoglobin; MCA, middle cerebral artery; MoM, multiples of the median; PSV, peak systolic velocity.

cardiothoracic ratio irregularities, and greater nuchal or placental thickness [202]. Advances are also being made in methods of noninvasive prenatal diagnosis (NIPD), which detects fetal DNA in the mother's plasma and is becoming more widespread in its availability [203].

### 9.3. Potential maternal complications for pregnancies with hb barts hydrops fetalis syndrome

The maternal mortality rate for women carrying a hydropic fetus who are not receiving adequate medical care nears 50% [204,205]. Historically, >60% of women carrying a fetus with Hb Barts hydrops fetalis syndrome develop hypertension during the pregnancy, 30% develop severe preeclampsia, and 11% develop antepartum hemorrhage [204,206]. Other serious complications may include worsening anemia, premature labor, placental abruption, oligohydramnios, potential miscarriage, renal failure, and congestive heart failure [205–208]. Postpartum complications can include retained placenta, hemorrhage, life-threatening hypertension, puerperal pyrexia, and anemia [209–211]. Thus, patients should be carefully monitored for these issues throughout the pregnancy and after delivery.

### 9.4. Pregnancy in patients with HbH disease

Key aspects of monitoring and management of pregnancy in patients with HbH disease are summarized in Table 1.

## 10. Novel therapies

### 10.1. Treatment targets

In patients with TDT, current development efforts are focused on reduction of transfusion requirements to ease the clinical, psychological, and economic burden of chronic transfusion and iron chelation therapy. In patients with NTDT, the aim is to improve Hb levels and ameliorate ineffective erythropoiesis and all downstream pathologic sequelae. Several novel therapies are currently in development with such treatment targets, including curative gene manipulation techniques and disease modifying agents that target ineffective erythropoiesis or hepcidin dysregulation.

### 10.2. Intrauterine allogeneic stem cell transplantation

Intrauterine allogeneic stem cell transplantation is currently an experimental approach that attempts to exploit the bidirectional maternal-fetal tolerance during pregnancy to correct the anemia before the baby is born. A single-center, non-randomized study (NCT02986698) enrolled fetuses with Hb Barts hydrops fetalis syndrome between 18 and 26 weeks' gestation diagnosed by chorionic villus sampling, amniocentesis, cordocentesis, or by identification of parents as genetic carriers, and identification of fetal anemia or signs of impending hydrops without a second major anatomic anomaly (not related to thalassemia) [212]. Fetuses underwent a single intrauterine

infusion of CD34+ cells from 300 mL of maternal marrow, followed by intrauterine red cell transfusion every 3 weeks. Two patients have undergone this procedure thus far. Both had low levels of engraftment. One patient showed reactivity against maternal antigens, while the other was offered but declined booster transplant.

### *10.3. Gene therapy*

Early clinical studies are evaluating the safety and efficacy of autologous HSCT using autologous $CD34^+$ HSCs transduced with a lentiviral vector encoding the human α-globin gene for treating transfusion-dependent patients with α-thalassemia (HGI-002 [NCT05851105]; GMCN-508 A [NCT05757245]).

#### *10.3.1. Disease modifying agents*

Mitapivat is an oral, small-molecule allosteric activator of the RBC-specific form of pyruvate kinase (PK) that leads to increased adenosine triphosphate (ATP) production in RBCs and improves their survival in thalassemia mouse models [213–215]. Mitapivat is approved in the US for the treatment of hemolytic anemia in adults with PK deficiency and in the EU for the treatment of PK deficiency in adult patients. In an open-label, multicenter phase 2 study, 20 patients with NTDT (α-thalassemia, $n = 5$; β-thalassemia, $n = 15$) and Hb levels ≤10 g/dL received mitapivat 50 mg twice daily for 6 weeks and then 100 mg twice daily for 18 weeks [90]; 80% ($p < 0.0001$) showed a Hb response, defined as Hb levels increasing ≥1.0 g/dL from baseline at ≥1 assessments between weeks 4 and 12, inclusive [90]. An Hb response was observed in all 5 patients with α-thalassemia. Improvements in markers of hemolysis and ineffective erythropoiesis were also seen. Mitapivat was well tolerated in this study, and global phase 3 trials of mitapivat for treating adults with TD α-thalassemia and β-thalassemia (ENERGIZE-T; NCT04770779) and NTD α-thalassemia and β-thalassemia (ENERGIZE; NCT04770753) are ongoing. The efficacy and safety of another PK activator, etavopivat, is currently being studied in patients with α-thalassemia, β-thalassemia, or sickle cell disease in a phase 2 trial (NCT04987489).

As a result of ineffective erythropoiesis, hepcidin expression is suppressed through various erythroid factors, resulting in increased iron absorption and primary iron overload [216,217]. Hepcidin is under the negative control of transmembrane serine protease 6 (TMPRSS6) [218]. Theoretically, inhibition of TMPRSS6 expression could increase hepcidin production and reduce anemia and iron overload [219]. A phase 1 single-dose study of a small interfering RNA (siRNA) conjugate (SLN124) optimized for hepatic targeting of TMPRSS6 is being conducted in adults with NTD α-thalassemia and β-thalassemia (NCT04718844).

Luspatercept, a recombinant fusion protein comprising a modified extracellular domain of activin receptor type IIB fused to the FC domain of human IgG1, is an erythroid maturation agent (ie, affects late-stage erythropoiesis) approved to treat anemia secondary to β-thalassemia in adult patients requiring regular RBC transfusions (US and EU) as well as those with NTD β-thalassemia (EU) [220–222]. The efficacy and safety of luspatercept in adult patients with HbH disease is presently being studied in a multinational phase 2 clinical trial (NCT05664737).

## 11. Conclusion and future considerations

α-Thalassemia is a genetic disorder with complex pathophysiology and multi-organ involvement. There is a need for heightened awareness of α-thalassemia in the medical community so that accurate diagnosis, early intervention to treat complications, and successful management of the condition is achieved. Beyond the treating hematologist or PCP, a multi-disciplinary team of experts is needed for monitoring and to deal with emerging complications in vital organs. Collaborative research efforts are also needed to establish the evidence-base on disease epidemiology and unmet needs, to support the continued development of novel therapies and management approaches.

### Practice points

- In patients with α-thalassemia, globin chain imbalance leads to ineffective erythropoiesis and hemolysis, resulting in chronic anemia, iron overload, and associated short- and long-term complications.
- There is a direct correlation between a patient's genotype (number of α-globin genes affected, with deletional or nondeletional mutations) and severity of clinical phenotype.
- Blood transfusion is the only available intervention for patients with symptomatic anemia, while iron chelation therapy is indicated in patients with evidence of iron overload (due to increased intestinal absorption or regular transfusion therapy).

### Research agenda

- Development of local disease registries to inform epidemiology.
- Establishment of collaborative longitudinal cohorts to evaluate disease outcomes, treatment patterns, and risk factors for morbidity and mortality.
- Development of novel therapies targeting the underlying genetic anomaly or the ineffective erythropoiesis.

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All authors contributed to manuscript conceptualization, critical review of all drafts, and provision of suggestions on the scientific content. The authors retained full editorial control and provided final approval on all content.

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### Data sharing and data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this review.

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