REVIEW ARTICLE

Hemoglobinopathies

Clinical Manifestations, Diagnosis, and Treatment

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SUMMARY

Background: Hemoglobinopathies are among the most common inherited diseases around the world. They have become much more common recently in northern and central Europe, including Germany, due to immigration.

Method: Selective review of the literature with consideration of national guidelines.

Results: The hemoglobinopathies encompass all genetic diseases of hemoglobin. They fall into two main groups: thalassemia syndromes and structural hemoglobin variants (abnormal hemoglobins). α- and β-thalassemia are the main types of thalassemia; the main structural hemoglobin variants are HbS, HbE and HbC. There are many subtypes and combined types in each group. The highly variable clinical manifestations of the hemoglobinopathies range from mild hypochromic anemia to moderate hematological disease to severe, lifelong, transfusion-dependent anemia with multiorgan involvement. Stem-cell transplantation is the preferred treatment for the severe forms of thalassemia. Supportive, rather than curative, treatment consists of periodic blood transfusions for life, combined with iron chelation. Drugs to treat the symptoms of sickle-cell disease include analgesics, antibiotics, ACE inhibitors and hydroxyurea. Blood transfusions should be given only when strictly indicated. More than 90% of patients currently survive into adulthood. Optimally treated patients have a projected life span of 50 to 60 years.

Conclusion: Hemoglobinopathies are a public health issue in today's multiethnic German population. Adequate care of the affected patients requires a wide variety of diagnostic and therapeutic measures.

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With approximately 7% of the worldwide population being carriers, hemoglobinopathies are the most common monogenic diseases and one of the world's major health problems (1, 2, e1, e2). They were originally found mainly in the Mediterranean area and large parts of Asia and Africa (3). International migration has spread them from those areas all over the world. In many parts of Europe today, hemoglobin (Hb) defects are classified as endemic diseases (3) *(Table 1)*.

Germany is one of the countries in which hemoglobinopathies have increased in recent years (4–7). There are no epidemiological studies on their frequency. The following statements can be made regarding gene carriers: prevalence among the 9 million immigrants from countries with a high risk of hemoglobinopathies as a whole is 4.5%, giving a figure of 400 000 for the number of hemoglobinopathy gene carriers (6). The total number of patients diagnosed with these diseases in the author's laboratory from 1970 to 2010 is 5831.

This review article should be considered an extension of the original article "Hemoglobinopathies in Germany—a longitudinal study over four decades," also published in *Deutsches Ärzteblatt International* (6). It aims to provide a brief summary of the most important clinical pictures and indicate the features that can be used to identify those with these diseases with low-level symptoms, but not gene carriers in good health, in general practice *(Tables 2, 3)*. Topical grounds for the publication of this article are the increase in the number of people affected, which has implications for care provision, and the fact that optimum treatment can give patients a steadily-increasing projected life span. As a result, medical treatment is becoming more and more part of adult medicine, rather than pediatrics alone.

Indications for hemoglobin testing

Hemoglobin testing is particularly indicated in the following situations (8, 9):

- Microcytic hypochromic anemia after iron deficiency has been ruled out
- Chronic hemolytic anemia
- Vascular obliteration crises of unclear etiology in patients from areas in which HbS and/or HbC is widespread
- Drug-induced anemia
- Erythrocytosis and/or cyanosis caused by hematological factors

- Hydrops fetalis of unclear etiology
- Prevention (testing of family members, diagnosis of partners for genetic counseling)
- Prenatal diagnosis.

Generalized hemoglobin electrophoresis for all cases of anemia cannot be justified on the basis of expediency or financial considerations, particularly in those with no background of migration.

Diagnosis

Hemoglobinopathy diagnosis in routine practice involves a red blood cell (RBC) count with erythrocyte indices, and a hemoglobin test (hemoglobin electrophoresis and/or chromatography) *(Tables 2, 3)*. Specialized tests in facilities qualified for the purpose are often required (6, 9, 11, e3, e4). The *eFigure* shows a testing plan for step-by-step diagnosis and also includes indications for DNA testing.

Basic types of hemoglobinopathy

The umbrella term "hemoglobinopathy" includes all genetic hemoglobin disorders. These are divided into two main groups as follows:

- Thalassemia syndromes
- Structural hemoglobin variants (abnormal hemoglobins).

Both are caused by mutations and/or deletions in the α- or β-globin genes. When gene defects cause Hb synthesis disorders, this gives rise to thalassemia. Hemoglobin structure in these cases is normal. When they cause changes in Hb structure, this gives rise to abnormal hemoglobin (5, 6, 11). There are also many mixed forms that combine features of both groups, e.g. β^0/β^+-thalassemias, HbSC disease and HbE α-thalassemias. The common features of the pathophysiology and various disease patterns are limited, and as a result so are the possibilities for summarizing them.

Thalassemia syndromes

This term includes all thalassemic Hb synthesis disorders *(Table 2)*. These are autosomal recessive conditions. α- and β-thalassemias have the greatest clinical significance (5, 11, 12).

Heterozygous thalassemia carriers are not completely healthy: they always have symptoms that require clarification with mild, iron-refractory, microcytic hypochromic anemia. Homozygous major forms are accompanied by serious, hypochromic hemolytic anemias and complex diseases.

α-thalassemias

α-thalassemias are caused by an α-globin chain synthesis defect. At the molecular level, they result from partial (α^+) or total (α^0) deletions, or more rarely mutations, of one or more of the four α-globin genes (αα/αα). They occur mainly in Africa, Arab nations, and, more frequently, South-East Asia (5).

Diagnostic criteria and cardinal symptoms: there are four clinical pictures of α-thalassemia, according to the number of genes affected by loss of function (5, 12). All of them become manifest perinatally *(Table 2)*:

- Clinically inapparent α-thalassemia minima (heterozygous α^+-thalassemia, -α/αα). This can be identified on the basis of mild hypochromia revealed in a blood count, with a barely measurable reduction in Hb values.
- α-thalassemia minor (heterozygous α^0-thalassemia, --/αα, or homozygous α^+-thalassemia, -α/-α) with mild anemia, hypochromia, microcytosis.
- HbH disease (compound heterozygous α^+/α^0-thalassemia with three inactive α-genes, --/-α), moderate hypochromic hemolytic anemia with splenomegaly. Anemic crises are caused by viral infections and oxidants (drugs). Complications include cardiac problems, gallstones, lower leg ulcers, and folic acid deficiency.
- Hb Bart's hydrops fetalis (homozygous α^0-thalassemia) with very serious hemolytic anemia already present *in utero* and marked by a lack of any α-globin chain synthesis (--/--), with hydrops and ascites. This is fatal if not treated.

β-thalassemias

β-thalassemia syndromes *(Table 2)* are the result of insufficient (β^+) or absent (β^0) production of β-globin chains. Their molecular causes are β-globin gene mutations. Most patients come from Mediterranean countries, South-East Europe, Arab nations, and Asia. Hematological changes become manifest from between the ages of three months and six months onwards (5, 6, 13).

Diagnostic criteria and cardinal symptoms:

- Thalassemia minor (heterozygous β-thalassemia) with mild, microcytic hypochromic anemia (2)
- Thalassemia intermedia (mild homozygous or mixed heterozygous β-thalassemia) of moderate severity and with a varying need for transfusions; typical complications are skeletal deformities and tumorous masses as a result of massive hyperplastic erythropoiesis (2)
- Thalassemia major (severe homozygous or mixed heterozygous β-thalassemia) (13) with long-term, transfusion-dependent anemia *(Table 4)*; untreated children die before the age of 10. Thalassemia major entails a risk of iron overload and multiorgan involvement. As a result of treatment, the full clinical picture is no longer seen in Germany (2, 13). Optimally treated patients have a projected life span of 50 to 60 years.

Abnormal hemoglobins

This group of autosomal dominant inherited hemoglobin disorders is caused by structural defects resulting from an altered amino acid sequence in the α or β chains (3, 10, 14). Clinicians must distinguish between clinically harmless Hb abnormalities and those that cause illness *(Table 3)*. These latter are divided into the following four well-defined groups:

- Variants with a tendency to aggregate and with sickle cell formation, e.g. the sickle syndromes (14)

TABLE 1

Prevalence of hemoglobinopathy gene carriers in the world's population (1–3, 6, e1, e2)

Region	Gene carriers
Africa	5 to 30%
Arab nations	5 to 40% Up to 60% regionally
Central Asia and India	10 to 20%
South-East Asia	5 to 40% Up to 70% regionally
USA and Central America	5 to 20%
Italy	7 to 9%
Greece	6 to 7%
Turkey	7 to 10%
Germany, Great Britain, Portugal, Spain, France, the Netherlands, Belgium, Scandinavian countries	Among total population: 0.5 to 1% Among immigrants: 5%
Albania, the former Yugoslavia, Croatia, Bosnia-Herzegovina, Bulgaria	2 to 5%
Russia	Rare
Transcaucasia	Up to 5%

- Variants with abnormal hemoglobin synthesis, e.g. HbE (2, 10)
- Variants with a tendency to precipitate and with hemolysis (unstable hemoglobins), e.g. Hb Köln (15)
- Variants with abnormal oxygen transportation and congenital polycythemia, e.g. Hb Johnstown (16, 17), or with congenital cyanosis (abnormal methemoglobins, HbM abnormalities, e.g. M Iwate) (2).

The forms in the third and fourth groups cause serious illness when heterozygous. When homozygous, they are fatal.

The main Hb abnormalities, both worldwide and among immigrants living in Germany, are HbS, HbC, and HbE. The large groups of rare Hb abnormalities that occur only in isolated cases all over the world should also be monitored. These are often accompanied by hemolysis, polycythemia, and/or cyanosis. Identifying these is an important part of differential diagnosis of hematological diseases where other efforts towards diagnosis have proved inconclusive (3, 6, 10, 11).

HbS and sickle-cell disease

The term "sickle-cell disease" includes all manifestations of abnormal HbS levels (proportion of HbS >50%). These include homozygous sickle-cell disease (HbSS) and a range of mixed heterozygous hemoglobinopathies (HbS/β-thalassemia, HbSC disease, and other combinations) (14).

According to the International Nomenclature, the previously commonly-used term "sickle-cell anemia" should not be used, as the dominant aspects of the disease are vascular obliterations and the organ damage they cause, not anemia.

HbS is the most dangerous of all hemoglobinopathies. The sickle cells caused by a lack of oxygen lead to vascular obliterations, so infarctions with tissue death can occur in almost all organs (skin, liver, spleen, bone, kidneys, retina, CNS). Chronic hemolytic anemia can usually be well tolerated (14). Aplastic crises are seen with severe anemia following viral infections (2).

Diagnostic criteria and cardinal symptoms: Symptoms begin before the age of one, with chronic hemolytic anemia and developmental disorders *(Table 3)*. The main problems are pain crises (sickle-cell crises) that can affect the back, extremities, thorax, abdomen, and CNS in particular. Patients are also dangerously susceptible to infection, particularly by pneumococci, hemophilus, salmonellae, klebsiellae, and mycoplasmae. Sepsis, osteomyelitis, and meningeal events, sometimes with cardiac involvement, frequently result in death. Spleen crises, acute thoracic syndrome (ATS), and strokes are also fatal in more than a few cases. These issues cause serious organ damage.

Optimally treated patients can have a projected life span of 50 to 60 years.

Heterozygous HbS gene carriers are not affected clinically or hematologically (18).

HbC abnormality and HbC disease

HbC homozygosity, or HbC disease, progresses in a similar way to sickle-cell disease, but is less serious (2, 3). Variable hemolytic anemia is the most dominant form. Heterozygous HbC gene carriers enjoy complete clinical health *(Table 3)*.

HbE abnormality and HbE disease

HbE is an extremely common Hb variant native to South-East Asia. Its disease pattern is similar to that of β-thalassemias. Hb is also unstable, which means that hemolysis can be caused by viral infections and medications *(Table 3)*. HbE is often combined with thalassemias, which may result in serious major-form hemoglobinopathies (2, 3, 10).

HbE homozygosity (HbE disease): Typically, this is moderate, microcytic hypochromic anemia with possible hemolysis due to exogenous causes.

HbE heterozygosity: Patients have variable hypochromic anemia similar to that found in β-thalassemia minor.

Treatment for β-thalassemias

β-thalassemia major

After being diagnosed, patients should be referred to a hematology center for counseling and to decide on

TABLE 2

Diagnoses, gene types, hematological findings, and cardinal symptoms of thalassemia syndromes (2, 4, 9)

Inheritance status/diagnosis/ phenotype	Arrangement of α-globin genes	Red blood cell count	Hemoglobin pattern	Cardinal symptoms
α-thalassemias				
Normal findings	αα/αα	Hb normal, MCH normal	Normal	No symptoms
Heterozygous α^+-thalassemia = α-thalassemia minima	– α/αα	Hb normal, MCH <27 pg	Normal	No symptoms Slight changes to blood count
Homozygous α^+-thalassemia = α-thalassemia minor	– α/– α	Hb normal or low, MCH <26 pg	Normal	Mild anemia Significant changes to blood count
Heterozygous α^0-thalassemia = α-thalassemia minor	– –/αα	Hb normal or low, MCH <24 pg	Normal	Mild anemia Significant changes to blood count
Mixed heterozygosity, α^+/α^0-thalassemia = HbH disease	– –/– α	Hb 8 to 10 g/dL, MCH <22 pg	HbH ≈ 10 to 20%	Variable chronic hemolytic anemia
Homozygous α^0-thalassemia = Hb Bart's hydrops fetalis	– –/– –	Hb <6 g/dL, MCH <20 pg	Hb Bart's 80 to 90%, Hb Portland ≈ 10 to 20%, HbH <1%	Life-threatening fetal anemia Generalized hydrops
β-thalassemias				
Heterozygous β-thalassemia = β-thalassemia minor	β^{++} β^+ β^0	Hb ♂ 9 to 15 g/dL Hb ♀ 9 to 13 g/dL MCV 55 to 75 fl MCH 19 to 25 pg	HbA_2 >3.2% HbF 0.5 to 6%	Mild anemia
Homozygous β-thalassemia = β-thalassemia major Compound heterozygous β-thalassemia = β-thalassemia major	β^+/β^+ β^0/β^0 β^+/β^0	Hb <7 g/dL MCV 50 to 60 fl MCH 14 to 20 pg	HbA_2 variable HbF 70 to 90%	Severe illness with long-term transfusion-dependent anemia
Mild homozygous or compound heterozygous β-thalassemia = β-thalassemia intermedia	β^+/β^+ β^+/β^{++} β^+/β^0 β^0/β^0 + influential factors	Hb 6 to 10 g/dL MCV 55 to 70 fl MCH 15 to 23 pg	HbA_2 variable HbF up to 100%	Moderate disease Variable transfusion dependency

treatment, and, if appropriate, for regular diagnosis appraisal *(Table 4)*.

The current international standard treatment (18–20) is based on the results of studies conducted at large sites in England (5) and the USA (3) and is stated in available child and adolescent medicine guidelines (20) (AWMF/II/025–017.htm).

Curative treatment: Hematopoietic stem-cell transplantation is the first-line treatment if a donor can be found (21).

Supportive treatment: Supportive treatment for thalassemia major includes lifelong regular transfusions combined with effective iron removal (20). Hemosiderosis-related organ damage requires specific treatment (22, 23).

- Transfusion therapy: Repeat hemoglobin concentration levels of less than 8 g/dL are an indication for beginning transfusion therapy. The target baseline hemoglobin level is 9 to 10.5 g/dL. The recommended frequency of transfusions is usually one every three weeks. Transfusion volume is usually 12 to 14 mg/kg body weight (BW) with an RBC concentrate hematocrit of 60%. Target Hb levels are 13 to 13.5 g/dL.
- Drug treatment to remove iron (chelation therapy): Iron removal is indicated when serum ferritin concentration repeatedly exceeds 1000 ng/mL (20).
  - Iron removal using deferoxamine: Standard deferoxamine treatment is a daily subcutaneous infusion (over several hours) at a dose of (20) – 40 – (50) mg/kg BW, 5 to 7 days per week. Dose adjustment is based on monthly testing of serum ferritin concentration. Patients must be closely

TABLE 3

Diagnoses, gene types, hematological findings, and cardinal symptoms of the main hemoglobin disorders (2, 3, 10, 13)

Diagnosis	Gene type	Red blood cell (RBC) count	Hemoglobin pattern	Cardinal symptoms
Sickle-cell disease	HbSS	Hb 6 to 9 g/dL Normochromic sickle cells Positive hemolysis parameters	HbS = 55 to 90% HbA_2 >3.5% HbF = <10 to >20%	Sickle-cell crises/pain crises Acute organ syndromes Chronic hemolytic anemia
HbS heterozygosity	HbAS	Normal	HbS = 35 to 40% HbA_2 ≥3.5%	No apparent illness
Sickle-cell β^+-thalassemia	HbS β^+-thalassemia	Hb 9 to 12 g/dL Hypochromia, microcytosis	HbS >55% HbF >20% HbA_2 >3.5%	Variable, mild sickle-cell disease
Sickle-cell β^0-thalassemia	HbS β^0-thalassemia	Hb 6 to 10 g/dL Hypochromia, microcytosis	HbS >80% HbF <20% HbA_2 >3.5%	Severe sickle-cell disease
HbSC disease	HbSC	Hb 10 to 13 g/dL Target cells MCV <75 fl	HbS ≈ 50% HbC ≈ 50% HbF <5%	Weak symptoms of sickle-cell disease Chronic hemolytic anemia
HbC disease	HbCC	Hb 10 to 12 g/dL Target cells MCV <75 fl MCHC >35 g/dL	HbC >95% HbA_2 ≈ 2.5% HbF ≈ 0.5%	Pain crises Organ events Chronic hemolytic anemia
HbC heterozygosity	HbAC	Normal	HbC ≈ 50% HbA ≈ 47% HbA_2 = 3%	No apparent disease
HbE heterozygosity	HbAE	Hb normal or slightly low Hypochromia	HbE = 25 to 35%	Mild, hypochromic anemia
HbE disease	HbEE	Hb 10 to 14 g/dL High RBC count MCH 20 pg MCV 65 fl Target cells	HbE >95% HbA_2 ≈ 2.5% HbF <3%	Mild anemia Hemolysis caused by infections/ medical drugs
HbE β^+-thalassemia	HbE β^+-thalassemia	Hb low to varying degree Hypochromia Microcytosis	HbE + HbA_2 = 25 to 80% HbF = 6 to 50% HbA = 5 to 60%	Variable, intermediate, hypochromic anemia
HbE β^0-thalassemia	HbE β^0-thalassemia	Hb <8 g/dL MCV <60 fl MCH <22 pg	HbE up to 85% HbA_2 <5% HbF = 15 to 25%	As for β-thalassemia major
Hemoglobinopathies with unstable Hb	HbX = approximately 150 different variants HbX/HbA	Hb variable to significantly anemic; Heinz bodies; Hemolysis caused by viral infections/medical drugs	HbX ≈ 20% HbA_2 ≈ 3 to 4% HbF <5%	Variable, sometimes transfusion-dependent chronic hemolytic anemia
Abnormal hemoglobins with disruptions to O_2 transportation function	Multiple variants	Polycythemia Increased MetHb	Varies according to type of abnormality	Congenital cyanosis with HbM abnormalities Congenital polycythemia with Hb abnormalities with high O_2 affinity

TABLE 4

Initial diagnosis and schedule for monitoring as part of transfusion and iron removal therapy for β-thalassemia major (2, 20)

	When	From age
Initial diagnosis and counseling		
– Complete blood count		
– Ferritin, transferrin saturation		
– Hemolysis parameters		
– Hb testing, DNA testing if needed	On diagnosis	
– Blood groups		
– Family appraisal		
– Information on the disease		
– Genetic counseling		
– Complete blood count	Before and after each transfusion	
– Antibody detection test	Every two months	1 year onwards
– Serology: hepatitis B/C, HIV, CMV	Annual status assessment	1 year onwards
Iron metabolism		
– Ferritin, transferrin saturation	At every transfusion	1 year onwards
Liver function, liver iron		
– GOT, GPT, γGT, bilirubin (total/direct)	Annual status assessment	1 year onwards
– Albumin, cholinesterase, Quick	Annual status assessment	1 year onwards
– Liver iron (biopsy, MRI)	Biannual status assessment	10 years onwards
Cardiology		
– Echocardiography	Annual status assessment	1 year onwards
– ECG, long-term ECG	Annual status assessment	1 year onwards
– Cardiac MRI (if possible), chest X-ray	Annual status assessment	Adulthood
Endocrinology		
– Percentile growth curve	Every transfusion	1 year onwards
– Puberty stages, bone age/mineralization	Annual status assessment	10 years onwards
– Testosterone/estradiol, LH, FSH, prolactin, cortisol	Annual status assessment	13 to 15 years onwards
– Oral glucose tolerance test	Annual status assessment	10 years onwards
– Combined pituitary function test	Annual status assessment	10 years onwards
– Thyroid parameters	Annual status assessment	10 years onwards
– Serum calcium, phosphate	Monthly	10 years onwards

TABLE 5

Initial diagnosis and schedule for long-term monitoring of patients with sickle-cell disease (2, 18)

	When
Initial diagnosis	
– Complete blood count	On diagnosis
– Hb testing	
– DNA testing if needed	
– Ferritin, transferrin saturation	
– Blood groups	
– Hemolysis parameters	
– Family appraisal	
– Information on the disease	
– Genetic counseling	
Hematological tests	
– Complete blood count	At every doctor's appointment
– Ferritin, transferrin saturation	Annually
– Red blood cell antibodies	Before each transfusion
General clinical examination	
– Before the age of 6 months	Monthly
– 6 months to 1 year	Every two months
– 1 to 5 years	Every three months
– 5 years onwards, adults	Every four months
Examinations of specific organs	
Liver/gall bladder	
– Liver function	Annually
– Hepatitis: antibodies, antigen	Annually
– Ultrasound	Biannually
Kidneys	
– Urine testing	Annually
– Urea, serum creatinine	Annually
– Ultrasound (from 10 years onwards)	Annually
Heart	
– ECG	Biannually
– Echocardiogram	Biannually
Lungs (from 5 years onwards)	
– Chest X-ray	Biannually
– Lung function test	Biannually
– Blood gas test	Biannually
Eyes (from 10 years onwards)	
– Background	Annually
– Vision	Annually
Endocrinology	
– Thyroid	Annually
– Gonads	Annually

monitored for potential side effects of deferoxamine (reduced growth, bone damage, high-frequency hearing loss, retinal damage) (20).

– Iron removal with deferasirox: Deferasirox is a well-tolerated iron chelator in tablet form and has taken on a central role in iron removal therapy (22, 23). However, this is a relatively new drug of which no long-term studies have been conducted. A standard dose of 20 mg/kg BW/day is recommended for patients with β-thalassemia major who are receiving long-term transfusion therapy. This dose must be adjusted on the basis of monthly measuring of ferritin levels. The main side effects (close monitoring required!) are kidney failure, agranulocytosis, and liver failure (22, 23). Liver iron levels must be measured every two years *(Table 4)*.

- Splenectomy is indicated for tumorous enlargement of the spleen with increased need for transfusions and hypersplenism.

β-thalassemia intermedia

Transfusion therapy is indicated for patients with complications as a result of major increases in erythropoiesis, and patients with anemia and an inability to maintain stable hemoglobin levels of more than 8 g/dL. In such cases, lifelong continuous transfusion therapy should be considered, rather than transfusions at intervals, combined with appropriate chelation therapy (24).

β-thalassemia minor

For severe anemia, folic acid supplements (0.5 mg/day orally) may be considered (2). Iron supplements are contraindicated unless there is simultaneous iron deficiency.

Treatment for α-thalassemias

α-thalassemia minima and minor do not require treatment. Iron supplements are contraindicated (except in cases of iron deficiency) (20).

Treatment for HbH disease depends on the severity of the clinical picture, which can vary widely. Transfusions are rarely indicated. Anemia requires regular substitution with folic acid (e.g. 5 mg/week) (2, 20). Iron supplements are contraindicated (unless there is simultaneous iron deficiency).

For Hb Bart's syndrome, transfusions are required *in utero* and continuously after birth. Where possible, stem-cell transplantation is performed (12, 20).

Treatment for sickle-cell disease

Following diagnosis, patients should be referred to a hematology center for counseling and to decide on treatment, and, if appropriate, for regular diagnosis appraisal *(Table 5)*. The current standard treatment (18) is based on the results of studies conducted at large sites in England (5, e6, e7) and the USA (14) and is stated in available guidelines (18) (AWMF/II/025–016.htm).

Curative treatment

Allogeneic stem-cell transplantation may be used for children under 16 (21, e9). Indications are CNS infarction, particularly severe, frequent pain crises, or frequent occurence of acute thoracic syndromes. For older patients, transplantation is usually not an option due to a lack of donors and the high risks of transplantation.

Symptomatic treatment

- Analgesics: first-line treatment for pain crises consists of sufficient administration of fluids and analgesics appropriate to the level of pain (paracetamol, metamizol, possibly also codeine or tramal, or even morphine).
- With proteinuria above 0.5 g/24 hours, ACE inhibitors can inhibit progression of glomerulonephritis or glomerulosclerosis.
- Antibiotics are also administered, particularly for pneumococcal infection with suspected sepsis and for salmonella infection with suspected osteomyelitis.
- Hydroxyurea (18, e7, e8) is the only substance to date that can reduce the number and severity of pain crises (in 70% to 75% of patients) and decrease the number of episodes of acute thoracic syndrome and mortality. The initial dose of 15 mg/kg/day can be increased to 35 mg/kg/day. Due to severe side effects (18), sickle-cell patients may only be treated with hydroxyurea when it is strictly indicated, following patient education, if birth control is used (for women of reproductive age), with regular blood counts (initially every two weeks and then monthly), and with careful documentation of side effects. Side effects include cytopenia revealed in a blood count, hyperpigmentation, weight gain, opportunistic infections, azoospermia in approximately 80% of men (even years after the end of treatment), and marked hypomagnesemia. It is also believed that there is a teratogenic effect (18).
- Transfusion therapy is subject to strict indications (18). Unfortunately, these rules are often broken. Single transfusions are indicated for major splenic sequestration, aplastic crises, and acute thoracic syndrome, as well as before major surgery (Hb must be increased to 10 g/dL!). Partial exchange transfusions to reduce the proportion of HbS are indicated for acute organ failure or vascular occlusions, but rarely for refractory pain crises.
- The main indication for long-term transfusion programs (to maintain low proportions of HbS in the blood long-term) is a CNS infarction. Sickle-cell patients receiving frequent transfusions must receive chelation therapy.
- Splenectomy: homozygous sickle-cell diseases lead to spleen sclerosis and functional asplenia even in childhood. Patients with HbS β-thalassemia undergo splenectomy following splenic sequestrations or in the event of hypersplenism.

Prevention

Affected children must receive all vaccinations recommended by STIKO, Germany's Standing Vaccination Commission, and 7-valent pneumococcal vaccinations from the age of two months onwards (also see guidelines).

Prophylactic penicillin must also be administered from the age of three months onwards, for at least five years.

The most important guidelines for psychosocial treatment are stated in the *eTable*.

Evidence available on treatment for hemoglobinopathies

The evidence available in the literature is consistent and ranges from meta-analyses of controlled studies to field reports (5, 7, 13, 14). The evidence supports stem-cell transplantation (21), transfusion therapy (5, 7), and treatment for secondary hemosiderosis (22, 23) to treat thalassemias; and symptomatic treatment as a whole, including hydroxyurea treatment, to treat sickle-cell disease (8, 14, 25).

Conclusion

The projected life span and quality of life of patients with severe hemoglobin disorders can be significantly improved using advanced treatment methods. In contrast to other European countries, in Germany there is unfortunately still no comprehensive overall approach to optimum diagnosis and treatment strategies. One problem that has barely been addressed is continued treatment after patients have moved from pediatric or adolescent care to adult care. It would be particularly

KEY MESSAGES

- The umbrella term "hemoglobinopathy" includes all genetic hemoglobin disorders.
- The two main groups are thalassemia syndromes and structural Hb variants (abnormal hemoglobins). The main types of thalassemia are α- and β-thalassemia. The main types of abnormal hemoglobin are HbS, HbE, and HbC. Within these main types there are several subtypes, with differing disease patterns.
- Nowadays more than 90% of patients survive into adulthood. Optimally treated patients can have a projected life span of 50 to 60 years.
- Stem-cell transplantation is the first-line treatment for β-thalassemia major. Conventional treatment consists of lifelong transfusions, consistent iron chelation therapy, and long-term follow-up care.
- Treatment for sickle-cell disease focuses on treatment for pain crises/sickle-cell crises using effective analgesics and administration of fluids, and on the consequent antibiotic treatment of infections. Hydroxyurea treatment successfully reduces crises in many patients. Red blood cell transfusions are subject to strict indications. Organ damage must be treated as patients increase in age.

desirable to establish hemoglobinopathy care centers at which interdisciplinary teams care for patients, as happens in neighboring countries (25).

Conflict of interest statement
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REFERENCES

1. Weatherall DJ: Hemoglobinopathies worldwide: Present and future. Curr Mol Med 2008; 8: 592–9.
2. Kleihauer E, Kohne E, Kulozik AE: Anomale Hämoglobine und Thalassämie-Syndrome. Grundlagen und Klinik. Landsberg: Ecomed Verlagsgesellschaft 1996.
3. Steinberg MH, Forget BG, et al.: (eds.): Disorders of hemoglobin: genetics, pathophysiology and clinical management. Cambridge University Press 2001.
4. Kulozik AE: Hemoglobinopathies are on the increase. Dtsch Arztebl Int 2010; 107: 63–4.
5. Weatherall DJ, Clegg JB: The thalassaemia syndromes. 4th Edition. Oxford: Blackwell Science Ltd 2001.
6. Kohne E, Kleihauer E: Hemoglobinopathies in Germany—a longitudinal study over four decades. Dtsch Arztebl Int 2010; 107: 65–72.
7. Cario H, Stahnke K, Sander S, Kohne E: Epidemiological situation and treatment of patients with thalassemia major in Germany: results of the German multicenter-thalassemia study. Ann Hematol 2000; 79: 7–12.
8. Dickerhoff R, von Rücker A, Maschmeyer G, Heimpel H: Probleme erwachsener Sichelzellpatienten in Deutschland. Dtsch med Wschr 2009; 134: 1179–84.
9. Kohne E: Hämoglobinopathien. In: Thomas L (ed.): Labor und Diagnose. 8th edition. Frankfurt: TH-Books Verlagsgesellschaft 2011.
10. Weatherall DJ, Clegg JB, Higgs DR, Wood WG: The hemoglobinopathies. In: Scriver CR, Beauder AL, Sly WS, Valle D, Graw-Hill Mc. The metabolic basis of inherited disease. 8th edition. New York 2000.
11. Herklotz R, Risch L, Huber AR: Hämoglobinopathien – Klinik und Diagnostik von Thalassämien und anomalen Hämoglobinen. Therapeutische Umschau 2006; 1: 35–46.
12. Higgs DR, Weatherall DJ: The Alpha Thalassaemias. Cell Mol Life Sci 2009; 66: 1154–62.
13. Olivieri NF: The ß-Thalassemias. N Engl J Med 1999; 341: 99–109.
14. Steinberg MH: Sickle cell anemia, the first molecular disease: Overview of molecular etiology, pathophysiology, and therapeutic approaches. Sci world J 2008; 8: 1295–324.
15. Ohba Y: Unstable hemoglobins. Hemoglobin 1990; 14: 353.
16. Petrides PE, Beykirch MK, Kohne E: The high oxygen-affinity Hemoglobin Johnstown 109 (G11) ValLeu in a German kindred with an elevated erythrocyte hemoglobin conten: Potential interaction with HFE mutation. Blood Cells Mol Dis 2008; 40(2): 180–2.
17. Wajcman H, Galactéros F: Hemoglobins with high oxygen affinity leading to erythrocytosis, new variants and new concepts. Hemoglobin 2005; 29: 91–106.
18. Dickerhoff R: Sichelzellkrankheit. In: Leitlinien Kinderheilkunde und Jugendmedizin. I 1 2006; 1–7.
19. Kulozik AE: ß-Thalassämie: Bewährtes und Neues in der Diagnostik und Therapie. Mschr Kinderheil 1996; 144: 850–62.
20. Cario H, Kohne E: ß-Thalassämie, a-Thalassämie. In: Leitlinien Kinderheilkunde und Jugendmedizin. I 2a 2006; 1–11. I 2b 2006; 1–3.
21. Storb RF, Lucarelli G, McSweeney PA, Childs RW: Hematopoietic cell transplantation for benign hematological disorders and solid tumors. Hematol (Am Soc Hematol Educ Program) 2003; 372–97.
22. Gattermann N: The treatment of secondary hemochromatosis. Dtsch Arztbl Int 2009; 106: 499–504.
23. Cario H, Janka-Schaub G, et al.: Recent developments in iron chelation therapy. Klin Päd 2007; 219: 158–65.
24. Taher A, Isma´eel H, Cappellini MD: Thalassemia intermedia: revisited. Blood Cells Mol Dis 2006; 37: 12–20.
25. Sickle Cell Society, London: Standards for the clinical care of adults with sickle cell disease in the UK 2008. www.sicklecellsociety.org.

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REVIEW ARTICLE

Hemoglobinopathies

Clinical Manifestations, Diagnosis, and Treatment

Elisabeth Kohne

eReferences

e1. Loukopoulos D, Kollia P: Worldwide distribution of beta-thalassemia. In: Steinberg MH, Forget BG, et al. (eds.): Disorders of hemoglobin: genetics, pathophysiology and clinical management. Cambridge University Press 2001.

e2. Giordano PC, Harteveld CL, Heister AJGM, Batelaan D, van Delft P, Plug R, Losekoot M, Bernini LF: The molecular spectrum of beta-thalassemia and abnormal hemoglobins in the allochthonous and autochthonous dutch population. Community Genet 1998; 1: 243–51.

e3. Kohne E: Diagnostik von Hämoglobinopathien. J Lab Med 2004; 28: 400–9.

e4. Huber AR, Ottiger C, Risch L, Regenass St, Hergersberg M, Herklotz R: Thalassämie-Syndrome: Klinik und Diagnose. Schweiz Med Forum 2004; 4: 947–52.

e5. Old JM: Screening and genetic diagnosis of haemoglobin disorders. Blood Reviews 2003; 17: 43–53.

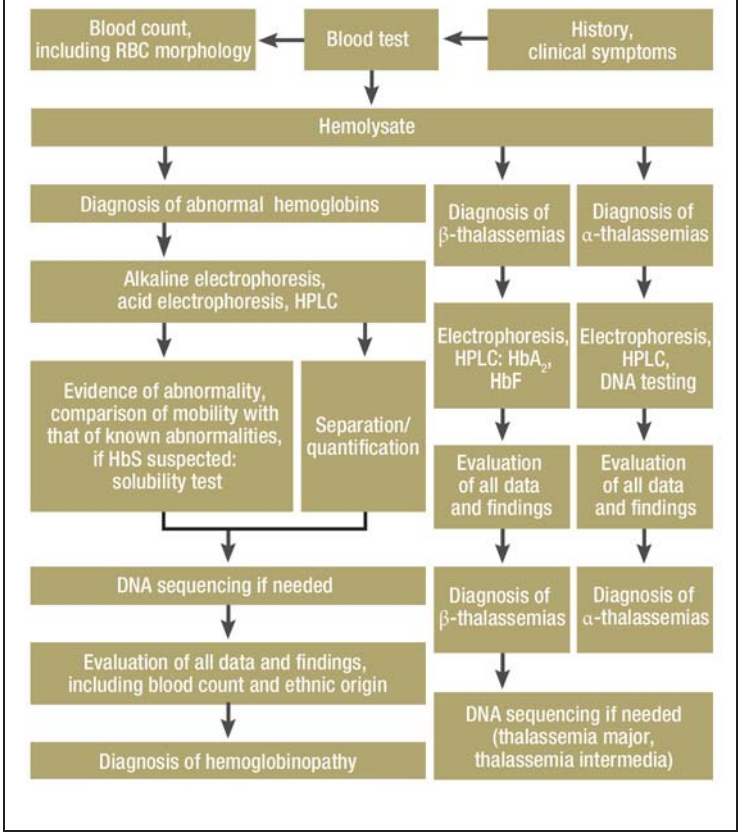
e6. Amrolia PJ, Almeida A, Halsey C, et al.: Therapeutic challenges in childhood sickle cell disease. Part 1: current and future treatment options. Br J Haematol 2003; 120: 725–36.

e7. Amrolia PJ, Almeida A, Davies SC, et al.: Therapeutic challenges in childhood sickle cell disease. Part 2: a problem oriented approach. Br J Haematol 2003; 120: 737–43.

e8. Platt OS: Hydroxyurea for the treatment of sickle cell anemia. N Engl J Med 2008; 358: 1362–9.

e9. Iannone R, Ohene-Frempong K, Fuchs EJ, et al.: Bone marrow transplantation for sickle cell anemia: Progress and prospects. Petiatr Blood Caner 2005; 44: 436–40.

eFIGURE



Indications for DNA testing

Hb abnormalities:
To identify rare abnormalities; for clarification in the absence of electrophoretic or chromatographic separation; as part of genetic enquiries (families, partners, prenatal diagnosis); mixed forms of more than one hemoglobinopathy.

Thalassemias:
To determine the genetic type of β-thalassemia major; molecular diagnosis of β-thalassemia intermedia; mixed forms of hemoglobinopathy; suspected silent β-thalassemia gene carriers; diagnosis of α-thalassemias; as part of genetic enquiries (families, partners, prenatal diagnosis).

RBC, red blood cell

eTABLE

Psychosocial support for patients with hemoglobinopathies

Main elements	
On diagnosis	• Comprehensive parent education and training • Psychological support: – Overcoming feelings of hurt and guilt – Developing a realistic, optimistic perspective
On beginning iron chelation therapy	• Practical help in learning how to perform treatment • Ensuring chelation is performed daily
During adolescence	• Dealing with psychosocial aspects of possible delay in maturation • Measures that promote compliance: – Regular availability to talk – Cooperation with treatment terms and measures – Involvement of patient in treatment-related decisions • Promoting contact with other affected adolescents and self-help groups • Availability of inpatient rehabilitation in appropriate hospitals
On career selection and incorporation into the workplace	• Encouragement to undertake qualified training according to individual inclination and abilities • Minimizing absences from training and work
Continuously	• Regular exchange of information on health-related and psychosocial problems