

Author
Dr John Evans
Associate Medical Director
SCOR Global Life

When red blood cells go wrong

Introduction

Red blood cell disorders occur as a result of a lack, an excess or a genetic defect in the production of these vital cells. A shortage of red blood cells, or erythrocytes, is evidenced by anaemia. According to the WHO, two billion individuals around the world are affected by **anaemia** and **iron deficiency** is said to be the cause of about half of cases.

Anaemia is an abnormal reduction in the concentration of haemoglobin in the blood. Its precise definition varies according to age and sex. Thus, the haemoglobin threshold in grammes per decilitre (g/dl) is 12.5 g/dl in non-menopausal women (13 g/dl after the menopause), 13.5 g/dl in men, 12.5 g/dl after the age of 80.

Several different mechanisms can lead to anaemia: a production disorder (insufficient erythropoietin synthesis), a deficiency due to accelerated destruction (hyperhaemolysis) or the loss of red blood cells (haemorrhaging). There are also some mixed forms of anaemia, most of which are a result of other conditions, cancer, chronic infectious or inflammatory diseases, for example.

Some forms of anaemia can only be diagnosed by doing a blood cell count: total red cell volume (TRCV) < 83 femtolitres (1×10^{-15} litres) indicates **microcytosis**; mean corpuscular haemoglobin (MCH) < 27 picogrammes is a marker of **hypochromia**; mean corpuscular haemoglobin concentration (MCHC) > 35% signifies **hyperchromia**, which is found in particular in **hereditary spherocytosis**; total red cell volume (TRCV) > 98 femtolitres indicates **macrocytosis**.

Genetic defects, which are responsible for hereditary anaemia, cause disorders such as drepanocytosis, commonly known as sickle cell disease, which causes severe chronic anaemia by destroying red blood cells (haemolytic anaemia). Thalassaemia in its different forms is the consequence of other genetic defects affecting haemoglobin synthesis and another defect lead to an excess of red blood cells or polycythaemia.

Some of these diseases have moderate effects that can be reversed by treatment, but they are always associated with high morbidity. Others are more severe and are life-threatening.

Editor
Gilles Meyer
life@scor.com

SCOR Global Life SE
Societas Europaea with
a capital of 274 540 000 €
5, avenue Kléber
75795 Paris Cedex 16
France
RCS Paris 433 935 558

www.scor.com

Expected Normal values for Erythrocytes

	Units	Children age ≤3 years	Male	Female
RBCs or Erythrocytes	Number in million/mm ³ or T/l (tera/litre)	4-5.2	4.5-5.7	4.2-5.2
Hemoglobin	g/dl g/l	12-14 120-140	13-17 130-170	12-15 120-150
Hematocrit	%	36-44	42-54	37-47
MCV m	µm ³ or fl (femtolitre)	74-88	80-100	80-100
MCH PG	(picogram)	24-30	27-32	27-32
MCHC	%	28-33	32-35	32-35
Reticulocytes	Number/mm ³ G/l (giga/l)	20 000-80 000 20-80	20 000-80 000 20-80	20 000-80 000 20-80

Source: Pharmacy Internship Contest, 8th ed. (February 2004) and Handbook of medical testing (5th ed. Maloine).

Deficient Erythropoiesis - Anaemia

Deficient Erythropoiesis means the body is not producing enough red blood cells. **Myelodysplastic syndromes** in the elderly are the typical example and can go as far as aplasia. Other causes of insufficient red blood cell production can be **congenital** (for example, thalassaemia) or **acquired (deficiency anaemia)**.

Iron deficiency, by far the most common cause, leads to microcytic and hypochromic anaemia (small red blood cells containing a low concentration of haemoglobin), but does not necessarily constitute an urgent medical problem, even at a very severe level as it is often well tolerated.

On the other hand, **Biermer disease**, a selective deficiency in vitamin B12 absorption in the intestines, which is responsible for macrocytic anaemia (larger than normal red blood cells), has a more guarded prognosis. Even after treatment and correction of the anaemia, close surveillance of the stomach is necessary (monitoring with upper gastrointestinal endoscopy every two years) to detect and provide early treatment of gastric cancer, a feared complication of Biermer's anaemia. However, the disease is benign when treated correctly.

In **iron deficiency anaemia**, only the cause of the bleeding or poor absorption is of any importance in the prognosis (gynaecological causes, digestive disorders, AVK drugs, gluten intolerance).

The prognosis for **myelodysplastic syndromes** is assessed according to several criteria: WHO classification, IPSS score (International Prognostic Scoring System), whether or not the subject is transfusion dependent, whether or not there is thrombopenia (a platelet count < 50 000/mm³ is a very negative prognostic factor), the severity of post-transfusion iron overload. Myelodysplastic syndromes are only rarely seen in insurance medicine.

And the **prognostic role of anaemia**? In a subject **without severe internal involvement** (for example cardiac insufficiency), the Hb transfusion threshold is 7-8 g/dl. The prognosis must take account of how fast the haemoglobin level drops. **In the event of severe internal involvement** the threshold rises to 10 g/dl. **Anaemia therefore does not necessarily have a prognostic role in itself.**

The **red blood cell**, otherwise known as a red corpuscle or erythrocyte, produced in the bone marrow, is the only cell in the body shaped like a biconcave disk. This gives it a much larger surface area than a round shape, so a larger contact surface and more space to exchange gases. Red cells have no nucleus, DNA, mitochondria, or intracellular organelles: this means they can be densely filled with haemoglobin. Haemoglobin, whose role is transport oxygen from the pulmonary capillaries to the tissues, is made up of haem and globin. Adult globin is a protein made up of four chains (two α and two β) each including a molecule of haem that contains one iron atom that can bind one O₂ molecule. Haemoglobin is therefore a tetramer with four ferric complexes which bind oxygen.

Chronic forms of anaemia Hyperhaemolysis

Hyperhaemolysis is related to an accelerated destruction of red blood cells.

Hereditary spherocytosis is a disorder of the red cell membrane and the most common of the congenital forms after sickle cell anaemia and the different types of thalassaemia. The other congenital forms are types of elliptocytosis and stomatocytosis. These are diseases with a good prognosis, where the only problems come from splenomegaly or the condition after splenectomy. Red blood cell enzyme deficiencies make their cellular metabolism more fragile. **G6PD deficiency** is the most common type (450 million people affected worldwide). There are three types with varying degrees of severity: type I which is very severe (leading to chronic haemolytic anaemia), types II and III in which patients can develop acute anaemia in states of oxidative stress, for example after taking certain medications or consuming fresh fava beans (favism). **When the restrictions on diet are followed and medication taken, types II and III are asymptomatic and the prognosis is not unfavourable.**

As for the **acquired forms**, these are **autoimmune haemolytic anaemia** and **paroxysmal nocturnal haemoglobinuria**. The main prognostic factors in **congenital haemolytic anaemia** are:

- **splenomegaly**: the size of the spleen exposes patients to a risk of rupture (care must be taken if practising combat sports, rugby, horse-riding) and acute hypersplenism,

- **splenectomy**: due to the risk of sepsis with encapsulated organisms, the patient must be vaccinated against pneumococcus and haemophilus and be given prophylactic antibiotic therapy. There is also an increased risk of venous thrombosis and pulmonary embolism,
- **acute erythroblastopenia due to parvovirus B19**: a one-off occurrence in the life of a patient, this can cause a significant drop in the haemoglobin rate,
- **the very haemolytic forms of malaria**: these lead to an increased risk of anaemia and haemolytic anaemia,
- formation of **chronic cor pulmonale following an embolism in patients who have had a splenectomy with persistent haemolytic anaemia**: this concerns stomatocytosis, unstable haemoglobin disorders, enzyme deficiencies,
- **constitution of severe iron overload** (the criterion of evaluation being an increase in the ferritin level),
- complications of biliary lithiasis secondary to haemolytic anaemia.

The prognosis for **acquired autoimmune haemolytic anaemia** depends on:

- duration and intensity of the immunosuppressive treatment, corticotherapy in particular,
- the causal or associated disease: haemolytic anaemia may be idiopathic or due to another disease.

When considering the prognosis for **paroxysmal nocturnal haemoglobinuria**, account must be taken of:

- wide variability in presentation and course,
- use of Eculizumab (monoclonal antibody), which inhibits the destruction of blood cells; but many other treatments are also available,
- the frequency of thromboembolic, infectious and iatrogenic complications.

Other types of anaemia caused by congenital haemoglobin disorders

Thalassaemia is a series of disorders characterised by a quantitative defect in the synthesis of haemoglobin chains, whereas **sickle cell disease** results from damage to its structure. The haemoglobin normally present in red blood cells is called haemoglobin "A". In subjects suffering from sickle cell disease, haemoglobin A is partly or totally replaced by a different type of haemoglobin, haemoglobin S, also known as sickle cell haemoglobin. Sickle cell haemoglobin is capable of deforming the red blood cell containing it to give the cell in question its characteristic «sickle» shape. It then loses its ability to circulate in the small blood vessels, which then get blocked; it interferes with the delivery of oxygen to the cells and is destroyed early.

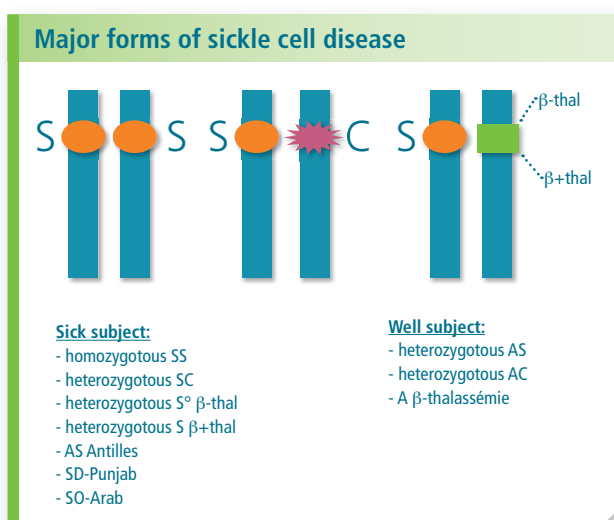
• Sickle cell anaemia

This disease is found in populations all over the world and there is a high prevalence in regions where malaria is endemic. In Africa, the prevalence of the sickle cell trait is higher than 30% in some places. The condition is also found in Sicily, Greece, southern Turkey and India. Over 2 million people in the United States carry the sickle cell trait. In France, sickle cell anaemia is the most common genetic disease. In fact, the disease now represents a major public health issue.

The sickle cell trait, the heterozygous form of sickle cell disease, **is totally asymptomatic**. The only restriction of carriers of this trait: **they should avoid altitudes above 3,000 m**.

Likewise, **people with heterozygous haemoglobin C, D and E traits are totally asymptomatic**. In these cases, there is no associated risk.

The mutation of the β globin genes, which causes sickle cell anaemia, leads to the synthesis of abnormal haemoglobin (HbS). **It is inherited as an autosomal recessive trait** and although heterozygous individuals (with sickle cell trait) do not suffer from full-blown sickle cell disease, the risk of a homozygous (symptomatic) child being born of heterozygous parents is therefore 1 in 4.



Sickle cell disease, the full-blown homozygous form, features deformed red blood cells with the crescent or sickle shape. It is also marked by a high level of replacement of erythrocytes, but each patient finds a balance between their production and their destruction and has his or her own haemoglobin rate. Being anaemic is not necessarily a sign of severity, what is more worrying is **the course of the anaemia over time**. Currently the only cure is allogeneic bone marrow transplant.

Complications

Acute complications include vaso-occlusive crises, acute chest syndromes, infections with encapsulated organisms, anaemia, splenic sequestration, priapism, deafness and blindness, cerebrovascular accidents.

Painful crises are a direct consequence of vaso-occlusion. This is the main cause of hospitalisation in adult patients suffering from sickle cell disease.

Acute chest syndrome is the reason for 20% of hospitalisations and is the leading cause of mortality in young adults.

Secondary prevention of strokes is provided by monthly blood transfusions.

Nephropathy, leg ulceration, cerebrovascular involvement, chronic liver involvement, cardiomyopathy, osteonecrosis, retinopathy and deafness are among the **chronic complications**.

Renal involvement is manifested by microalbuminuria, proteinuria, nephrotic syndrome, chronic renal failure developing over a period of years (generally after 40) and requiring haemodialysis and eventually a kidney transplant. Mortality associated with nephropathy is higher if dialysis begins at D+90 than immediately after the beginning of the procedure, **hence the interest of a rapid transplant**.

Proliferative retinopathy, however, has had a more favourable prognosis since the introduction of treatment by laser photocoagulation.

Concerning **leg ulceration**, this causes serious functional disability as well as disfigurement. Recurrences are very frequent and prevalence depends on the anaemia.

If diagnosed early, **osteonecrosis** can be treated simply: by bone marrow aspiration and reinjection to avoid the need for total hip or humerus replacement. This procedure has changed the prognosis for osteonecrosis.

The risks of acute complications, renal involvement, retinopathy, neurological involvement, leg ulceration make sickle cell anaemia a **similar condition to diabetes**.

Treatment

Whether or not a **disease-modifying treatment such as an exchange blood transfusion programme** is begun will depend on the status of the haemoglobin. Today this therapy is codified, but **haemochromatosis** is the major complication. The other treatment that has proved its worth is **hydroxycarbamide**, given long-term. **Hydroxycarbamide** has proven its effectiveness in reducing vaso-occlusive crises and acute chest syndromes, but also in reducing mortality after the age of 40.

Finally, treatment is based on five essential elements: **early detection and prevention and the treatment of acute complications** on the one hand, **prevention, early screening and treatment of chronic complications**, on the other. The introduction of a disease-modifying treatment must be considered on a case-by-case basis. Therefore, **the quality of the monitoring of the disease is a factor in better prognosis**. As for diabetes, **preventive management improves the occurrence of chronic complications and patient survival**.

Life expectancy is increasing regularly, with the improvement in care. There are no factors that predict severity at birth.

Case history to be taken into account and severity criteria proposed

The **prognosis** for sickle cell disease must take account of a certain number of elements in the case history: **periods in intensive care and how long ago they were** (an acute episode that occurred ten years ago cannot be compared with repetitive complications), **introduction of a long-term transfusion programme** (proof of a quite serious condition), **regular monitoring in a specialist centre** (positive criterion), **neurological involvement** (involvement of large vessels is a negative prognostic factor), **reduction in visual acuity or hearing**. The presence of **nephropathy with damage to kidney function**, of **cerebrovascular involvement**, a **lack of medical follow-up**, the introduction of a **long-term exchange transfusion programme**, the presence of **pulmonary hypertension** can be considered as **severity criteria**.

• α and β -thalassaemia

Prevalence of α -thalassaemia varies from 1 in 1,000 inhabitants in the countries of northern Europe to 1 in 10 in southern countries. In France, about 200 people suffer from a form that requires clinical care (α -thalassaemia). It is estimated that 100,000 children a year are born worldwide with a serious form of **β -thalassaemia and as many again for the clinical forms of α -thalassaemia.**

Thalassaemia is caused by point mutations (alterations in the α or β globin genes) which abolish or reduce the synthesis of the haemoglobin chain. Over 400 mutations have been identified. The severity of the disorder depends on the type of mutation. **The α and β -thalassaemia traits are also totally asymptomatic and the prognosis is not unfavourable.**

In **α -thalassaemia**, the α chains are produced in smaller quantities, which makes it impossible to make enough haemoglobin. In the case of **β -thalassaemia**, the β chains are produced in insufficient quantities or not at all (depending on the mutation), which also causes an insufficient production of haemoglobin, but the relative excess of the α chain constitutes a problem in β -thalassaemia.

There are three classes of β -thalassaemia, depending on the type of mutation and the patient's phenotype: major, minor (with no effect on life expectancy) and intermediate.

α -thalassaemia

Genotype	Phenotype	Hb	Bart's	Haematopoiesis
$\alpha\alpha/\alpha\alpha$		Normal		Normal
$\alpha\alpha/\alpha-$		Silent carrier		Normal
$\alpha\alpha/--$ (10% Asia)		α -thal trait	2-10% (NN)	Moderate microcytic anaemia
$\alpha/-/\alpha$ (7% Africa)				
$\alpha/-/--$		HbH 5-40% HbH	20-40% (NN)	Variable mycrocytic anaemia
$--/--$		Hydrops fetalis	100%	Lethal

β -thalassaemia

	Thal. major	Thal. intermedia	Thal. minor
Severity	++++	++	+
Splenomegaly	++++	++ to +++	0 to +
Bone abnormalities	++ to ++++	0 to ++	0
Hb level	<7g/dl	7-10g/dl	>10g/dl
Hypochromia	++++	+++	++
Microcytosis	+++	++	+
Polycythaemia	+++	0 to +	0 to +
Reticulocytes	Normal	↗ ↗	N

Heterogeneity of survival in thalassaemia major

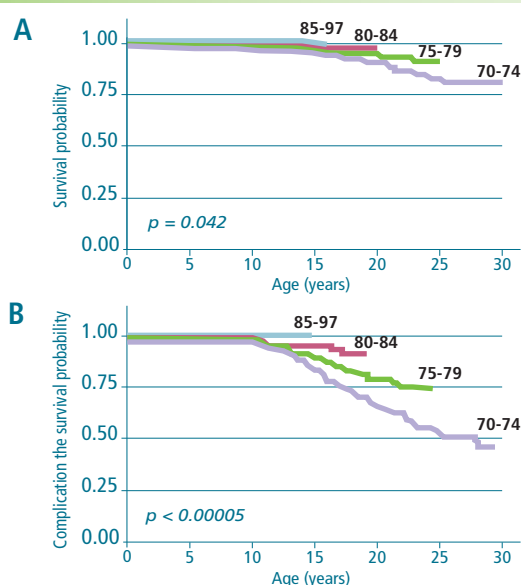


Figure A: Survival curves, from birth, of patients born after 1970, subdivided by birth cohort.

Figure B: Complication-free survival by cohort of birth. Patients born in later years had better complication-free survival, and developed the first complication later, although estimation beyond 15 years is not available for the cohort born in 1985 or later. Hypogonadism is not accounted for in the curves.

Source: Borgna Pignatti et al., Haemathologica 2004.

Thalassaemia major: basic treatment

Thalassaemia major is a severe form of β -thalassaemia that occurs early (in the first few months of life). Subjects suffering from it have a low haemoglobin rate, under 7 g/dl. The basic treatment consists of treating the anaemia by **regular transfusions, which may lead to secondary iron overload.**

The key element in prognosis

Iron overload can lead to multiple complications: cirrhosis, cardiomyopathy, endocrine disorders (diabetes, hypothyroidism, etc.). An **MRI scan** will show the deposits of iron in the liver and heart. **The treatment of the haemochromatosis is a key element in the prognosis.** This requires **well conducted chelation therapy from childhood onward.** As the risk of complications occurring is correlated with the ferritin level, **ferritinaemia > 2 500 mg/l is a negative prognostic factor.**

Polycythaemia

Polycythaemia is much less common, but more difficult to measure from an epidemiological point of view because of its primary or secondary origins. The incidence of polycythaemia vera varies between 5 and 20 cases per million individuals per year.

Polycythaemia is characterised by an elevation of the haemoglobin thresholds: >15.5 g/dl in non-menopausal women and >16.5 g/dl after the menopause, > 17 g/dl in men. It may be diagnosed when **haematocrit** is higher than 52% in men and 48% in women. Insofar as this parameter depends on the volume of plasma, a certain diagnosis requires proof of **a real excess mass of red blood cells**, total red cell mass per kg of lean body mass: a level > 36 ml/kg in men, > 32 ml/kg in women. This is generally done by **measuring the total red cell volume by the isotopic dilution method**.

Polycythaemia vera and relative polycythaemia

With a Haematocrit in excess of 60% in men and 56% in women, the probability of a diagnosis of **polcythaemia vera** is in excess of 80% and in any case will require treatment.

Below 55% and 50% respectively, in the great majority of cases, it will not be polycythaemia vera but haemoconcentration or **relative polycythaemia**. **Still called stress polycythaemia**, frequent in men over 50 (1%), this is nevertheless considered as a vascular risk factor.

The most common form of **polycythaemia vera** is **Vaquez's disease**. The average age of diagnosis is late, around 60 on average. Specific mutations must be sought (JAK-2 gene). **The higher the haematocrit, the greater the vascular risk** (a large number of patients are diagnosed when biological tests are done for strokes or other vascular accidents).

Polycythaemia vera is an **emergency**. The aim is to bring, by treatment (bleeding), the haematocrit below 45% in men and 42% in women. The clinical course may progress to myelofibrosis or leukaemic transformation after at least ten years.

Genetic polycythaemia

Very often familial, these types of polycythaemia are characterised by three mechanisms. The first concerns an **abnormality in the red blood cells' affinity for oxygen**. The second invokes **abnormalities in the response to erythropoietin (EPO)**. The

third is related to **disorders in the synthetic route of EPO**. An **increased level of EPO** in the blood orients the diagnosis in these cases. Their prognosis is good.

In conclusion...

Among the forms of deficiency anaemia, **iron deficiency** is not necessarily worrying, even at a very severe level. On the other hand, in **Biermer disease**, even after the anaemia is treated, long-term monitoring is essential.

Subjects who are carriers of the sickle cell trait (AS) carry no increased mortality or morbidity risk in relation to this defect.

As for diabetes, **preventive management of full-blown sickle cell disease** considerably improves the occurrence of complications. Generally speaking, **survival of sickle cell patients** has improved with treatment with hydroxyurea.

Subjects who are carriers of the thalassaemia trait (thalassaemia minor) carry no increased mortality or morbidity risk in relation to this defect. As for the **major forms of thalassaemia**, their prognosis depends on **good observance of the chelation therapy**. Globally, **survival of thalassaemia patients has improved** with parenteral and now oral iron-chelating agents.

The composite heterozygous forms SC and S β + thalassaemia, for their part, have a life expectancy close to normal. In **Vaquez's disease, the higher the haematocrit, the greater the vascular risk**. **Relative polycythaemia or stress polycythaemia**, on the other hand, should be considered a vascular risk factor in the same way as tobacco dependence is.

*Further guidance in the underwriting assessment of the conditions mentioned in this document can be found in **SOLEM**, SCOR Global Life's new online underwriting tool.*

Whilst compiling this document we have studied the prognosis for sickle cell disease and thalassaemia in conjunction with expert consultants from a unit specialising in the treatment of these diseases and as a result of these studies new decision procedures will soon be available for life insurance applicants with these disorders.

SOLEM is the fruit of SCOR Global Life's international expertise in risk selection; it is regularly updated thanks to work such as this, carried out by our research and development centre to provide you with the latest innovative solutions.

For more information on this subject, please contact your usual SCOR Global Life correspondents.