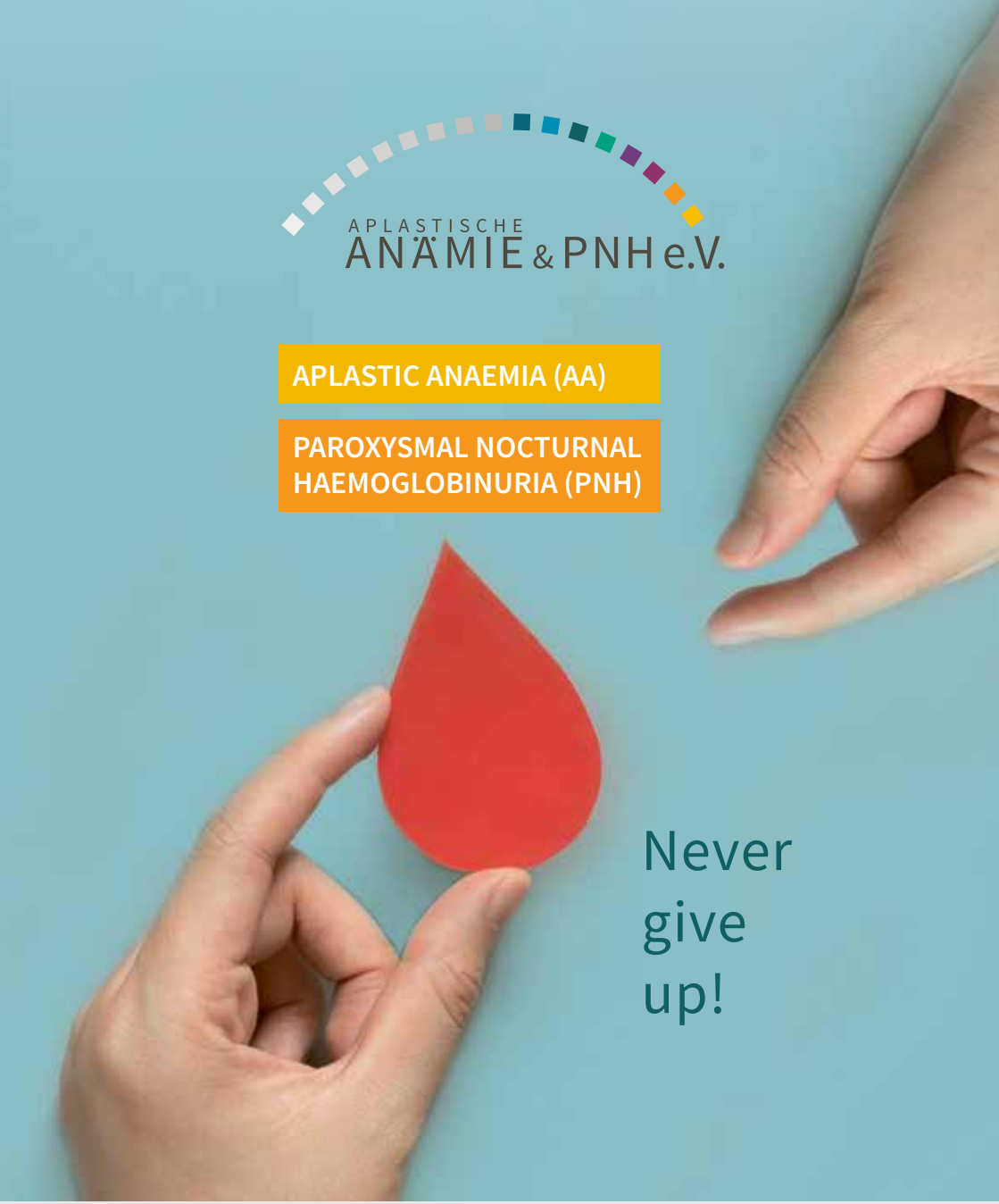
APLASTISCHE ANÄMIE & PNH e.V.

APLASTIC ANAEMIA (AA)

PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA (PNH)



Never give up!

Information for patients and relatives

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Postfach 52 03 25
12593 Berlin
Germany

Authors:
Dr. med. Ferras Alashkar
Rainer Göbel
Ulrike Göbel
Dr. med. Britta Höchsmann
Prof. Dr. med. Alexander Röth

Translation by:
Tracey Medical Translations
Dr David Tracey PhD DipTrans IoLET

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Designed and typeset by: Denise und Florian Malecki, degagee.de

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APLASTISCHE
ANÄMIE & PNH e.V.

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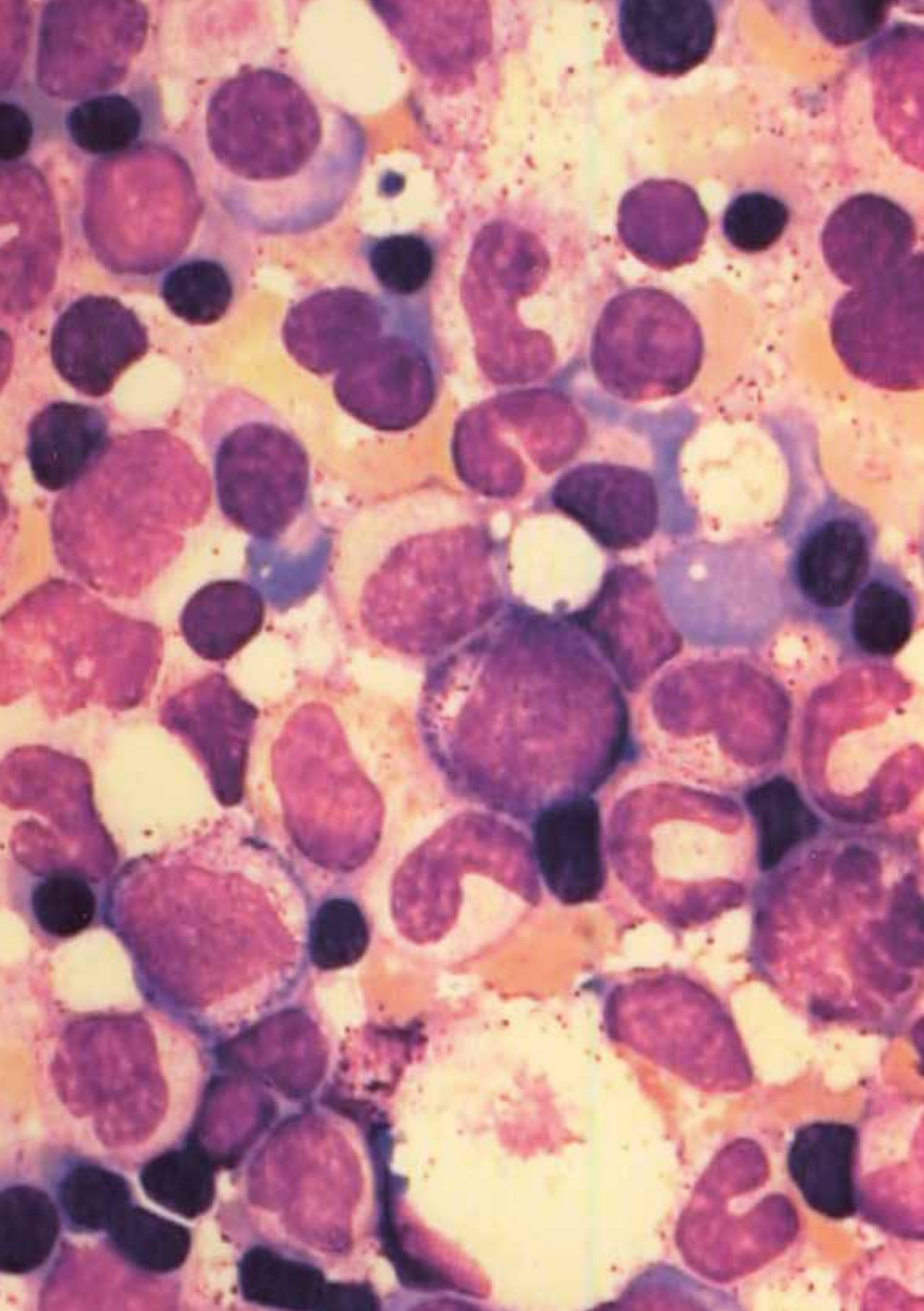
Foreword

Dear patients and relatives,

With this brochure we would like to inform you about the diseases „Aplastic anaemia“ (AA) and „Paroxysmal nocturnal haemoglobinuria“ (PNH). The brochure was written by experts in language that is understandable to laymen. It is intended to provide you with comprehensive knowledge of the development, diagnosis and treatment options related to these diseases. We want to provide you with the basis for a useful conversation between you and your doctor.
At the end of this brochure you will find a glossary with explanations of the most important technical terms, which we have marked in *italics* in the text. Do you have any questions or suggestions about this brochure or other issues? We would be happy to hear from you. Our contact details are at the end of this brochure.

We wish you all the best!



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Bone marrow

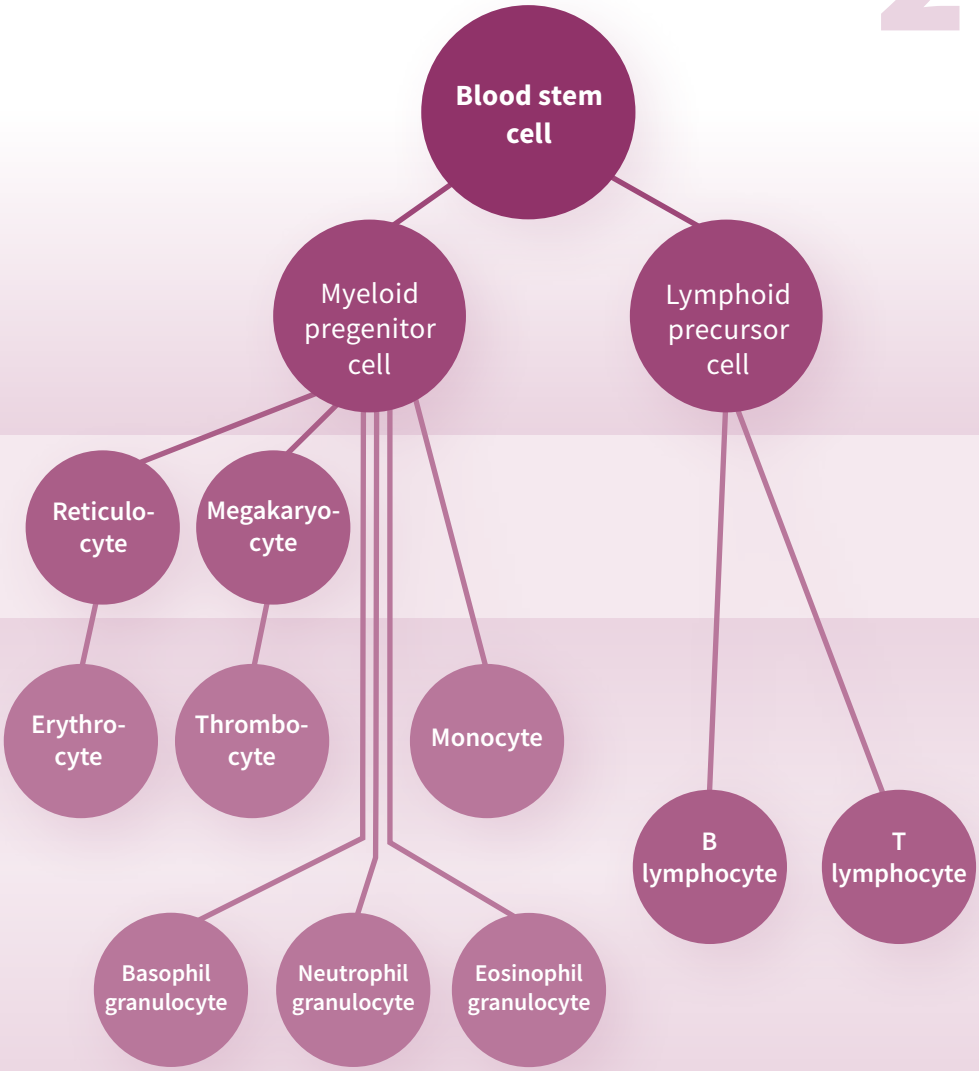
- Function
- Bone marrow stem cells
- Functional disorders

2 2.1 Function of the bone marrow

Inside the flat bones is the bone marrow, where all the blood cells are produced. There are three types of cell: **red blood** cells (*erythrocytes*), **white blood cells** (*leukocytes*) and **platelets** (*thrombocytes*).

- **Red blood cells** contain *haemoglobin*, which gives them their characteristic red colour. *Haemoglobin* is important for the transport of oxygen from the lungs to the body tissues and for returning carbon dioxide from the *periphery* back to the lungs.
- **White blood cells** form part of the *immune system*'s defences and protect the body against infection by viruses, bacteria, fungi. They can be divided into *granulocytes* and *lymphocytes*.
- **Platelets** help to stop bleeding.

The bone marrow constantly produces new blood cells, which enter the bloodstream once they have matured (see Fig. 1). They only have a limited lifespan: *erythrocytes* have a lifespan of about four months, *leukocytes* only a few hours and *platelets* a few days.
Normally, regulatory mechanisms produce as many new blood cells as the body needs. This means that the production of red cells can be increased if their number is reduced, for example due to *anaemia* or bleeding. If the body needs to fight an infection, the bone marrow produces more white blood cells.



↑ *Figure 1: Blood cell development (simplified)*

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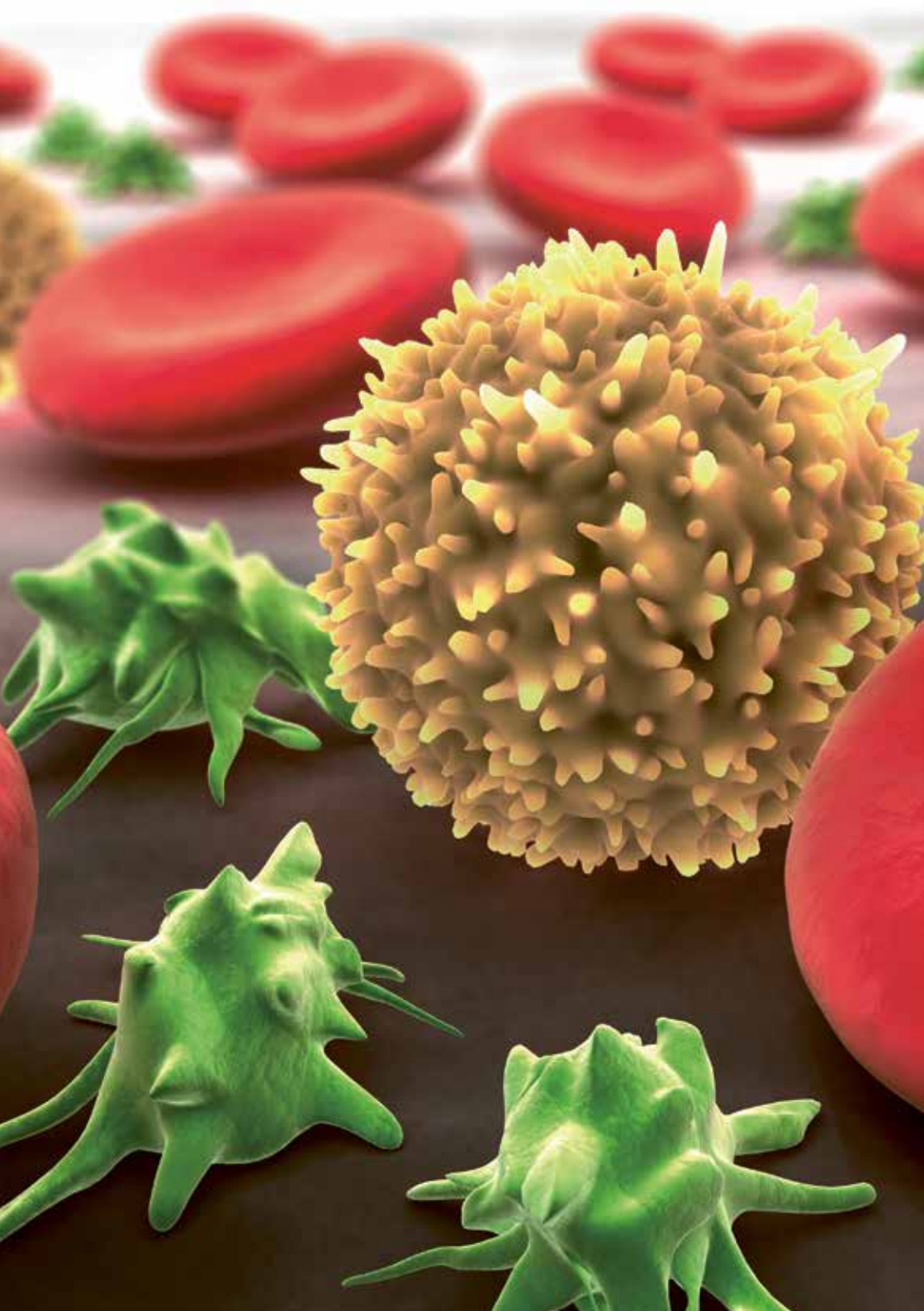
2.2 Bone marrow stem cells and their environment

The bone marrow contains a very small number of blood stem cells from which new blood cells are developed. Not only are fully mature cells produced, but new stem cells are constantly produced to maintain this ongoing cycle of cell generation.
If the stem cells are not damaged and the environment of the stem cells (the ‘stem cell niche’) is intact, normal production of healthy blood cells and stem cells can take place. But if either of these two components is defective, cell production is disrupted and there may even be complete bone marrow failure.

2.3 Functional disorders of the bone marrow (bone marrow failure)

If cell production in the bone marrow is disrupted, a sufficient number of blood cells cannot be produced (*bone marrow hypoplasia*). Depending on whether the production of *erythrocytes*, *leukocytes* or *platelets* is disrupted, symptoms such as pallor, a tendency to infection or bleeding can occur. If development of all three cell types is disrupted (*pancytopenia*), this is referred to as bone marrow failure (bone marrow aplasia).



3

Aplastic anaemia (AA)

- What is AA?
- Symptoms
- Diagnosis
- Clinical course
- Therapy
- Prognosis
- Registry

3 3.1 What is AA?

3.1.1 General information

Aplastic anaemia is a non-*malignant* haematological disease. It is due to a disorder of bone marrow function that results in reduced development of blood cells.
Aplastic anaemia can be divided into congenital forms (e.g. *Diamond-Blackfan* or *Fanconi* anaemia) and acquired forms, depending on the age at which it occurs. Acquired forms can occur at any age.

3.1.2 Occurrence (epidemiology)

The incidence of aplastic anaemia in Central Europe is 2-3 new cases per million people per year. Aplastic anaemia is therefore a very rare disease. Most people who are affected fall ill between the ages of 10 and 25 or above the age of 60, with both sexes being equally affected.

3.1.3 Origin (pathogenesis)

Studies have shown that a subtype of *lymphocyte* in the body‘s own *immune system* attacks cells in the bone marrow, and this autoimmune process prevents the development of new blood cells.
In most cases, it is not possible to identify the cause of aplastic anaemia, so the origin of the disease is still unknown (*idiopathic*). In some cases, medications, toxic substances or viral infections are thought to be the cause.

3.1.4 Diagnostic criteria and classification

In order to classify a disease as aplastic anaemia, the following criteria must be met:

- The number of cells in the bone marrow (*cellularity*) is less than 25% of that in healthy bone marrow, based on a bone marrow biopsy. Cell production may be reduced during the course of the disease (*hypoplastic*) or completely absent (*aplastic*).
- Reduction of two (*bicytopenia*) or three cell lines (*tri-* or *pancytopenia*) of varying degrees in the blood film.
- There is no evidence of (new) development of connective tissue in the bone marrow (*fibrosis*) or invasion of the bone marrow by *malignant* cells or cells outside the bone marrow.
- No radiotherapy or chemotherapy has been carried out recently that might explain a disorder of bone marrow function (*bone marrow insufficiency*).
- In addition, there have been no significant cell changes (*dysplasia*) in blood development (*haematopoiesis*).

Aplastic anaemia is subdivided according to blood values (see Table 2) into: **Non-severe**, **severe** and **very severe aplastic anaemia** and is of crucial importance for prognosis and therapy.

		Neutrophils	Platelets	Reticulocytes
nSAA	**Non-severe aplastic anaemia** = nSAA („**n**on-severe **AA**“)	< 1,0 G/l	< 50 G/l	< 20 G/l
SAA	**Severe aplastic anaemia** = SAA („**s**evere **AA**“)	< 0,5 G/l	< 20 G/l	< 20 G/l
vSAA	**Very severe aplastic anaemia** = vSAA („**v**ery **s**evere **AA**“)	< 0,2 G/l *	< 20 G/l	< 20 G/l

↑ Table 2: Classification of aplastic anaemia based on the blood count (cell count and film). Two out of three criteria must be met.

**For classification as vSAA, the criterion granulocytes < 0.2 G/l must be met.*

3.2 Symptoms of AA

3.2.1 Anaemia

A reduction in oxygen-transporting red blood cells (*erythrocytes*) can cause weakness, *fatigue* and shortness of breath and even palpitations, especially during physical exertion. In addition, patients with anaemia often show paleness, especially in the palms of the hands, although the presence of paleness is not evidence of *anaemia*.

3.2.2 Increased susceptibility to infection

A reduced number of white blood cells (*leukocytes*) increases the risk of infection. Since the body‘s own defence system does not function sufficiently with a reduced number of *neutrophils*, a subtype of white blood cells, such an *infection* can take a life-threatening course within hours and lead to blood poisoning (septicaemia).
It is therefore important that you inform your doctor immediately if you develop a fever. A fever is defined as a body temperature of over 38°C measured in the ear twice within an hour or over 38.3°C measured once in the ear.

3.2.3 Bleeding

If the number of blood *platelets* (*thrombocytes*) is reduced, blood clotting may be impaired. This can lead to bleeding gums and *petechiae*, small punctiform bleedings in the skin, or bruises (*haematomas*). These can also occur spontaneously, i.e. without previous injury. In the case of impaired clotting, even a relatively slight bleeding or injury (e.g. during a visit to the dentist) can be serious. In the event of bleeding, you should therefore contact your doctor as soon as possible so that he can decide whether special measures (e.g. *platelet transfusion*) are necessary.

3.3 Diagnosis of AA

If one or more of the above complaints and symptoms are present, the family doctor will have a blood test done. If this reveals an irregularity in the blood count, the patient may be referred to a specialist in haematology and/or oncology.

A number of further examinations will be carried out in this case:

- Medical history (*anamnesis*), including the family history and a detailed record of any medications taken
- Physical examination, e.g. signs of *anaemia* or bleeding
- Cell studies
  - Microscopic differential blood count
  - *Reticulocytes*
  - PNH diagnostics (a PNH clone is detectable in up to 70% of AA cases), see Chapter 4.3
- Clinical chemistry
  - *Haemolysis* parameters: especially *LDH,* haptoglobin, bilirubin
  - Coagulation: quick value, PTT, fibrinogen
  - Liver function parameters: AST, ALT and AP
  - Renal function parameters: *creatinine*, uric acid
  - Blood sugar
  - Total protein, electrophoresis, immunoglobulins
  - Inflammation parameters: CRP
  - Vitamin B12 and folic acid levels
  - Iron status: *ferritin*. At *ferritin* values > 1000 ng/ml further clarification of possible organ damage due to possible iron overload

- Virus diagnostics: hepatitis A, B, C; HIV, EBV, *CMV*, Parvovirus B19
- Antinuclear and anti-DNA *antibodies*

- Functional diagnostics
  - Ultrasound (*sonography*) of heart and upper abdomen
  - X-ray examination of the chest (*thorax*)
  - ECG
- Special investigations
  - *HLA typing* of the patient and his siblings
  - In cases of suspected „congenital“ bone marrow insufficiency syndrome, further diagnostic tests, e.g. chromosome breakage analysis in case of suspected *Fanconi anaemia*, *telomere* length determination if *telomeropathy* is suspected, genetic tests

If a reduced number of one or more blood cell lines is confirmed without any known cause for increased damage or breakdown of these blood cells, an urgent bone marrow examination should be carried out. This will help to determine whether there is a disorder of blood development or another cause.

For this purpose, a *bone marrow puncture* is performed, which can be done on an outpatient basis. A bone cylinder is usually taken from the pelvis under local anaesthetic using a hollow needle (*Jamshidi needle*) (*bone marrow biopsy*, bone marrow punch). This cylinder is approx. 1.5 cm in length with a diameter of 2-3 mm and is examined and evaluated under a microscope (*histology*).

In addition, blood, bone marrow and yellow marrow fragments are obtained with *bone marrow aspiration*. These are spread out over a glass microscope slide, dried and stained. They are then assessed under the microscope, whole and in their position in relation to each other (*cytological* examination).

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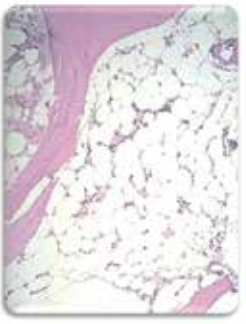
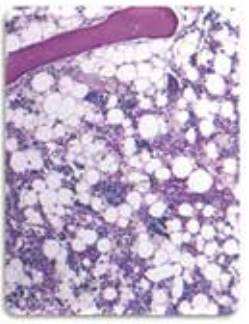
Furthermore, genetic tests can be carried out on the bone marrow cells, and the results of these tests can help to distinguish between diagnoses.
As the individual laboratory steps in preparing the bone marrow *histology* are time-consuming, it takes about 1-2 weeks to obtain a complete result. If the development of two or three cell lines (*erythrocytes, leukocytes, platelets*) is impaired according to the diagnostic criteria in Section 3.1.4 without the presence of pathologically altered cells (e.g. leukaemia cells) and without prior chemotherapy or radiotherapy, the disease is referred to as aplastic anaemia.

Bone marrow in aplastic anaemia



Healthy bone marrow



↑ Figure 3: Bone marrow in a patient with aplastic anaemia compared with healthy bone marrow. In the diseased bone marrow one can see mostly connective tissue and fat cells. In the healthy marrow, the blood cells stand out from the large white fat cells as small coloured dots.

The aim of these numerous investigations is to:

- Exclude other diseases
- Discover the possible causes (*aetiology*)
- Determine the severity of the aplastic anaemia
- Determine the prognosis

In patients with severe or very severe aplastic anaemia who are in good physical condition, it is advisable to carry out *HLA typing* of the patient as soon as the condition has been diagnosed. If the patient has siblings, they can also be typed to determine their suitability for stem cell donation.

3.4 Clinical course of AA

Without specific therapy, aplastic anaemia is fatal in up to 70% of cases in adulthood.
Aplastic anaemia may develop into myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML). In addition, some AA patients have a PNH-specific mutation.

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3.5 Therapy of AA

3.5.1 Overview

Haematological spontaneous healing (spontaneous *remission*) only occurs very rarely in cases of severe bone marrow failure.

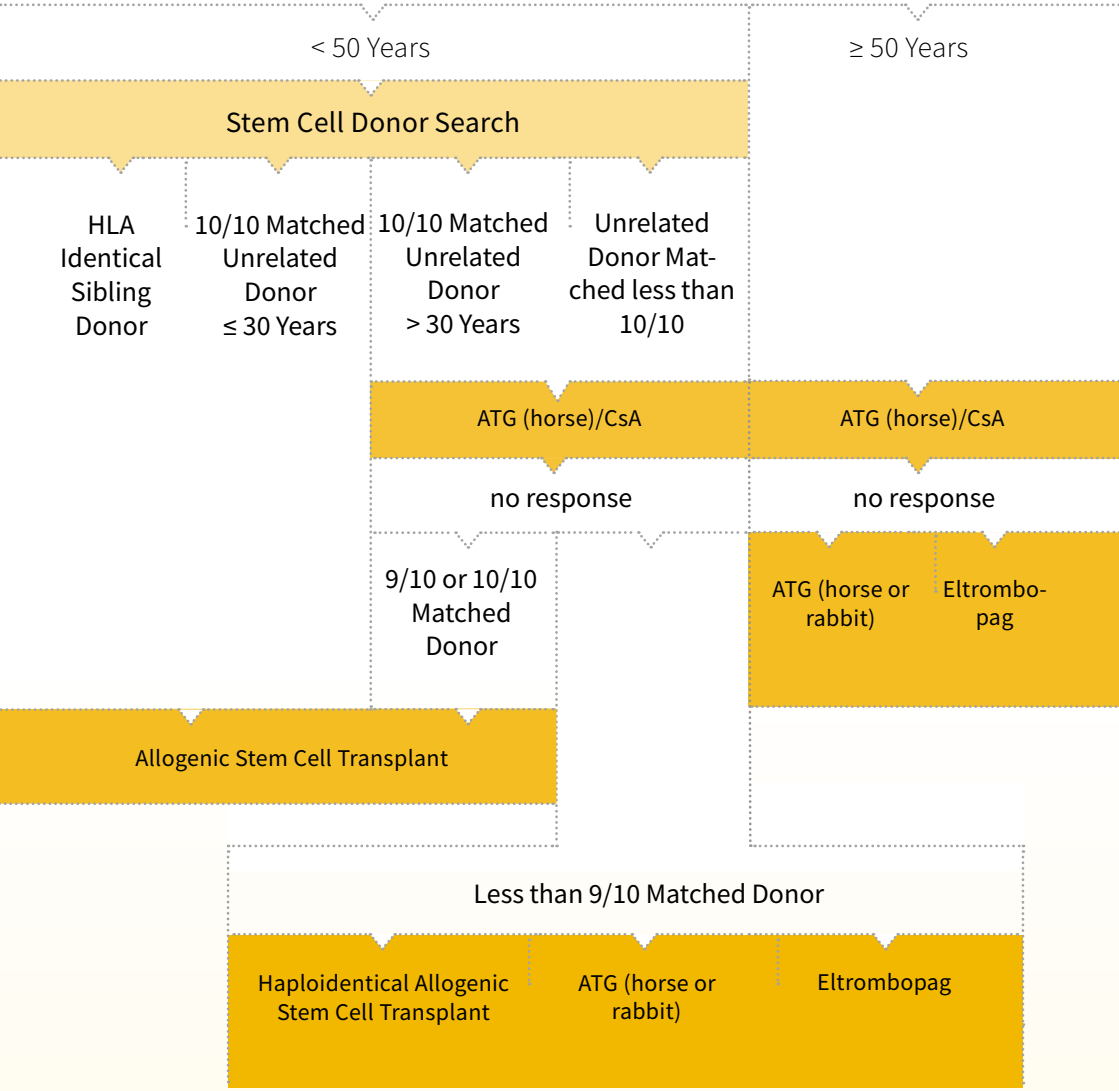
Treatment is needed for:

- Very severe (vSAA) and severe aplastic anaemia (SAA)
- Non-severe aplastic anaemia (nSAA) with a marked reduction in at least one cell line (*cytopenia*), which requires regular *transfusions* or leads to a risk of infection or bleeding
- Transition (progression) from an nSAA to an SAA

If the patient has nSAA, one can usually apply 'watchful waiting' without intensive therapy.

While a few decades ago there was hardly any prospect of a cure or long-term improvement, there are now promising options. Two main types of treatment are available: *immunosuppressive* therapy (IST), and stem cell transplantation (SCT) or bone marrow transplantation (BMT). In addition, there are specific treatments for certain subgroups of patients. Which of these is appropriate depends on the severity of the disease, the patient's age and possible concomitant diseases -- as well as the degree of the *HLA* match (*HLA compatibility*) with the potential bone marrow donor, whether related or unrelated.

Therapy algorithm aplastic anaemia
(vSAA, SAA, nSAA in need of therapy, no telomeropathy)



↑ *Figure 4: For the complete algorithm, please visit https://www.onkopedia.com/de/onkopedia/guidelines/aplastische-anaemie/@@guideline/html/index.html*

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If therapy is indicated, treatment should be started as soon as possible to avoid the progression of the disease and its possible complications (e.g. pronounced *anaemia*, infections, bleeding and coagulation disorders). Early therapy planning in cooperation with a specialised centre is therefore important.
The course of therapy for patients with severe or very severe aplastic anaemia and for patients with nSAA who require treatment is shown in Figure 4.

3.5.2 Immunosuppressive therapy (IST)

Antithymocyte globulin (ATG) and ciclosporin (CsA)
Since in aplastic anaemia the body's own *immune system* turns against its own bone marrow, *immunosuppressive* therapy is often indicated, especially in the case of:

- Patients with vSAA or SAA > 40-50 years
- Patients without *HLA-identical* (sibling) donors
- Patients with nSAA at risk of severe *cytopenia* in at least one cell row

- **Current data show that serum obtained from horses (equine *ATG*, horse *ATG*, h*ATG*) is significantly more effective than rabbit *ATG* (r*ATG*). However, the only approved horse *ATG* (h*ATG*) preparation (Lymphoglobulin®) was withdrawn from the market in the EU in 2007, so the medication must currently be imported from outside the EU. Due to the lack of approval in the EU, it is advisable to clarify the responsibility for costs in advance with the respective health insurance company. A new approval of equine/horse *ATG* in the EU has been applied for by the manufacturer, but not yet decided.**

Immunosuppressive therapy is usually a combination of the drugs *antithymocyte globulin* and *ciclosporin*. This allows the bone marrow to recover. In the course of the therapy, the blood count usually deteriorates for a short time before there is an improvement. The most common complications are fever or allergic reactions and rarely infections.
ATG is an *antibody* that destroys the overactive, bone marrow-damaging T *lymphocytes*. *ATG* is usually given for 4-5 days as an *infusion* into a large *vein* via a central *venous* catheter (CVC). During *ATG* therapy, the *platelet* count should be elevated to 30 G/l or kept there by means of *platelet transfusion*, if necessary, as the *platelet* levels can drop rapidly during therapy. For an *ATG* therapy, an inpatient stay of about 1-2 weeks must be expected. Side effects of *ATG* therapy can be allergic reactions such as skin rash and fever. To suppress acute side effects of *ATG*, a cortisone preparation, e.g. prednisone or prednisolone, is also administered for a short time.
Ciclosporin, which inhibits the release of immunostimulants, is another key factor in the therapeutic response to the disease. *CsA* is subject to regular laboratory tests to ensure that the optimal effect is achieved by adjusting the dose, if necessary. The aim is to achieve a minimum concentration of 100-200 ng/ml in the blood. For a stable effective level, the medication should be taken very regularly at fixed intervals of 12 hours.
Possible side effects of *CsA* therapy are infections, deterioration in kidney function, increased blood pressure, gum growth (*gingival hyperplasia*), increase in hair growth or tremor.

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CsA is taken as a capsule or juice for at least 12 months. To ensure a good and stable response to therapy, it is important that discontinuation involves reducing the dose of *CsA* very slowly and gradually in order to prevent a relapse. However, in some patients, *CsA* needs to be given for a longer period or even permanently to maintain the success of the therapy.
By intensifying *immunosuppressive* therapy, a cure (*complete remission, CR*) or at least a marked improvement (*partial remission, PR*) can be achieved in about 50-75% of patients, with *transfusion* independence and a significant reduction in the risk of infection and bleeding. It takes about 2-4 months, in some patients even 6 months, until an improvement of the blood values occurs. In most cases complete normalisation of blood values cannot be achieved.
If there is no response, a repeat of the *immunosuppressive* therapy can be considered after 4-6 months.
The risk of a relapse of the disease (*recurrence*) was about 35% earlier, when slow *CsA* tapering was still uncommon. The risk of relapse is lower with very slow *CsA* reduction. In the event of a relapse, a repeat of the *immunosuppressive* therapy is possible, as the chance of a renewed response is 30-60%.

In addition to specific therapy, every patient should receive supportive therapy (see Chapter 3.5.5).

Alemtuzumab

There are also other drugs that work through the same mechanism of *immunosuppression*. These include alemtuzumab, an *antibody* that works against T *lymphocytes*. This drug is used to treat chronic lymphocytic leukaemia (CLL) or multiple sclerosis (MS), but it has also shown good response rates in trials of aplastic anaemia, especially in older patients. One advantage of this drug is that it is only injected under the skin, so no hospital stay is necessary. If the patient previously had an infection with the *cytomegalovirus* (*CMV*), this blood value should be checked regularly, as this viral infection can reoccur under therapy.

Patients who did not respond to other therapies showed response rates of 37-48% when treated with alemtuzumab.

3.5.3 Allogeneic transplantation

In patients up to the age of approximately 50 years with severe or very severe aplastic anaemia (SAA or vSAA) and availability of a sibling donor who is fully compatible with the patient with respect to compatibility markers (*HLA*) (*HLA-identical*), the preferred treatment (*first-line therapy*) is an allogeneic transplantation.

Patients younger than 18 years of age can also receive stem cells from an unrelated *HLA-identical* donor (foreign donor) if they do not have an *HLA-identical* family donor. It is important that 'fine mapping' is performed and that donor and recipient are completely identical in this regard.

In recent years, the complication rate for *HLA-identical* foreign donor transplantation has been significantly reduced, so that it is increasingly used - especially in patients up to 40 years of age who do not respond to *immunosuppressive* treatment.

The aim of allogeneic transplantation is to replace the patient's non-functional bone marrow with healthy stem cells from a donor. To achieve this, the patient's bone marrow is first destroyed by various measures (chemotherapy, *antibody* therapy, radiation). This *conditioning* is carried out in the days immediately before the transplantation.

In parallel, new, healthy stem cells are collected from a healthy, related or unrelated volunteer.

Stem cells can be obtained directly from the bone marrow with *bone marrow biopsy* under anaesthesia. The punctures in the iliac crest for bone marrow collection may cause bruising and pain that may last for several days. In addition, there is the general anaesthetic risk.

Alternatively, the donor is injected with a drug that stimulates *granulocyte* development (*G-CSF*) over several days. The increased number of blood stem cells produced in this way migrate from the bone marrow into the blood. These 'peripheral blood stem cells' (PBSC) are then removed with a special device (*apheresis*), as in a blood plasma donation. The procedure can lead to flu-like symptoms and pain.

If the stem cells are obtained directly from the bone marrow, this is called a bone marrow transplantation (BMT). If the stem cells are obtained by *apheresis*, this is called a stem cell transplantation (SCT).

Studies suggest that treatment of aplastic anaemia with stem cells from *peripheral* blood may be associated with increased complications such as *acute* or *chronic* rejection. If possible, stem cells obtained directly from the bone marrow should therefore be used.

Regardless of the method of obtaining the stem cells, they are purified and examined for infectious agents. The patient then receives the healthy stem cells. The transplantation itself is like a blood *transfusion*. If everything goes well, the donor stem cells „grow" and lead to normal bone marrow function and blood development. An inpatient stay of at least four weeks is required for a transplant.

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During the transplantation, the patient receives *prophylactic* medication to prevent infections caused by bacteria and fungi. In addition, a cortisone preparation, e.g. prednisolone, and *ciclosporin* (*CsA*) are administered to influence the *immune system* for several months.

Potential complications due to the transplantation are:

- Toxic side effects during *conditioning* therapy
- Infections
- *Graft versus Host-Disease (GvHD)*
- Transplant rejection

- ***Graft versus host disease (GvHD)*: Here the donated *immune system* reacts against the body's own cells. This can be short term (*acute*) or long lasting (*chronic*), so that under certain circumstances permanent suppression of the *immune system* (*immunosuppressive* therapy) may be necessary.**

3.5.4 Further therapy options

Danazol
Some patients with aplastic anaemia have a rare congenital disorder in which the ends of the chromosomes (*telomeres*) are shortened, which is called *telomeropathy*. The shortening of the *telomeres* results in disrupted cell division and thus to reduced development of blood cells in the bone marrow.

Danazol, a synthetic variant of the male sex hormone testosterone, may cause the *telomeres* to lengthen, which can lead to an improvement in symptoms and even normal blood development.

Eltrombopag (Revolade®)
Eltrombopag has been approved for adult patients with acquired severe aplastic anaemia (SAA) since 2015 if they:

- have not responded to previous *immunosuppressive* therapy, or
- have received intensive pre-treatment and
- are not suitable for bone marrow or stem cell transplantation

Eltrombopag acts to control the development of blood stem cells and *platelets*. The medication activates *thrombopoietin* which controls the development of *platelets* and blood cells (*haematopoiesis*). The initial dose is 50 mg/day (maximum dose 150 mg/day). In the authorisation trial, it was shown that the use of eltrombopag led to an improvement of *platelet, erythrocyte* and *neutrophil* levels in some patients. Eltrombopag resulted in an improvement or normalisation of bone marrow *cellularity*. Patients who had previously

required regular *transfusions* had an increased number of days until the next *transfusion* or became *transfusion*-independent. Due to the very good response rates in clinical trials, eltrombopag has already been approved in the USA in combination with h*ATG* and *CsA* for *first-line treatment* of aplastic anaemia. An application for approval in the EU has also been filed.

Other

Therapies without proven efficacy, e.g. steroid *monotherapy* or *monotherapy* with *haematopoietic* growth factors, should be avoided, as they only mean loss of time and can significantly worsen the initial situation of the patient with regard to one of the proven therapeutic options.

3.5.5 Supportive therapy

Blood transfusions

Transfusions are necessary for many patients to ensure adequate physical fitness and quality of life and to avoid bleeding complications. They can temporarily replace the missing blood cells in case of corresponding symptoms (*anaemia*, bleeding). Not all of the blood is *transfused*, but only the type of cell that is needed (red blood cells or *platelets*).

- **To do this, the blood is examined after a blood donation to rule out transmissible infections. The white blood cells are then removed, and finally the various blood components are separated and concentrated. Family members are not allowed to donate blood, as these so-called directed donations pose particular risks.**

In order to ensure satisfactory tolerance, the preparation used is not only selected according to blood group (A, B, AB, O) and rhesus factor, but each individual preparation is tested individually for each patient. For this purpose, in a compatibility test or 'cross-matching', the patient's blood is mixed with blood from the *packed* red blood cells (P*RBCs*) and examined. Especially if antibodies are present, it can take longer to find suitable PRBCs. If a patient is *cytomegalovirus* (*CMV*) negative and there is a possibility of a later bone marrow or stem cell transplantation, *CMV*-negative concentrates should be given.

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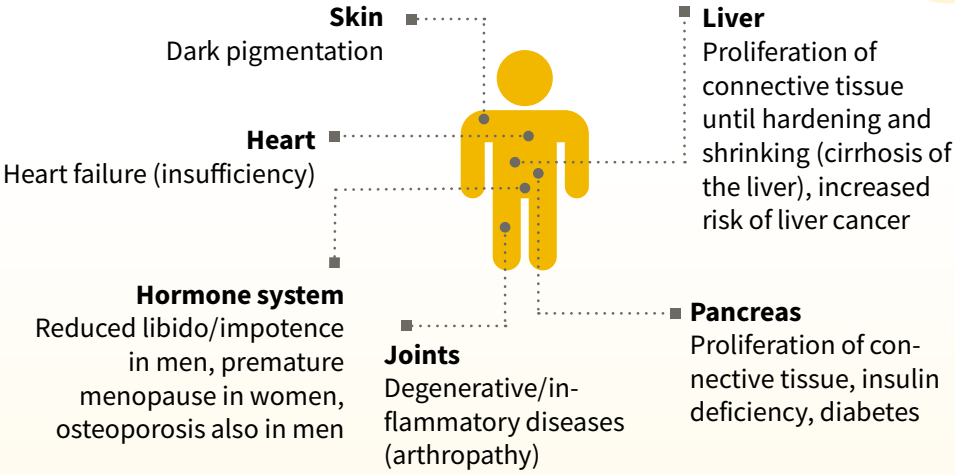
In general, packed red blood cells should be used with caution, as they can lead to the body being overloaded with iron. ***Indications* for a *transfusion* are:**

- Pronounced reduction in stamina associated with *fatigue* or in the context of shortness of breath, e.g. under physical exertion, and depending on the respective concomitant diseases, e.g. heart failure
- A very low *haemoglobin* level (< 7 g/dl)

Each unit of packed red blood cells absorbs more than 100 times the amount of iron than is taken in daily with food. As the human body cannot actively excrete iron, it is deposited in various organs, especially the liver, heart, kidney and bone marrow (see Table 5) and can damage them. Patients with aplastic anaemia or myelodysplastic syndrome (MDS) are particularly at risk because the impaired bone marrow function already decreases the development of new red blood cells and the iron cannot be used completely for the development of new ones.
As a rule, in the first few months after diagnosis, no storage iron (*ferritin*) or liver iron levels are reached which require immediate therapy to bind and excrete the excess iron (*chelation therapy*). It is therefore advisable to wait at least 6 months after initiating *immunosuppression*. If there is a continuing need for regular *transfusions* and serum *ferritin* levels are above 1,000 µg/l, *chelation therapy* is indicated. This is especially true for transplant candidates, as iron overload is associated with higher transplant-related mortality and morbidity.



↑ *Table 5: Complications of iron overload*

The drugs used today to treat iron overload are generally well tolerated. The major side effects include nausea, *diarrhoea* and renal dysfunction, but these disappear after discontinuation.

If the serum *ferritin* is permanently below 500 µg/l and there is *transfusion*-related iron overload, interrupting treatment may be considered depending on individual *transfusion* needs. However, this should always be done in consultation with the treating doctor.

■ **Further information on this issue can be found in the brochure „Transfusionsbedingte Eisenüberladung“ from German Leukaemia & Lymphoma Aid: www.leukaemie-hilfe.de/infothek/eigene-publikationen/informationsbroschueren**

3

Infections

In the case of febrile infections, a doctor should be consulted as soon as possible to make a diagnosis and initiate therapy. In certain cases, the preventive use of antibiotics against bacteria and of antimycotics ('against fungi') can be useful. **In addition, if the *granulocyte/neutrophil* count is low (< 0.5/nl), various behavioural measures should be observed:**

- Avoid contact with people who have infections
- Avoid close physical contact with animals
- Avoid large crowds, especially in the winter months
- Carry out usual hygiene measures, e.g. washing hands, oral hygiene, and ensure freshness and cleaning of raw food
- Avoid close contact with fungal spores, especially gardening, do not clean organic waste bins or turn compost

In very rare cases, e.g. severe infections, the use of the *haematopoietic* growth factors *G-CSF* or GM-CSF to stimulate the body's immune defence or the *transfusion* of white blood cell concentrates (*granulocyte* concentrates) may be considered.

- **You can find more detailed information in the German brochure „Infektionen? Nein, danke!" by M. Exner and A. Simon and the German Leukaemia & Lymphoma Aid: www.leukaemie-hilfe.de/infothek/eigene-publikationen/informationsbroschueren**

Bleeding

In case of bleeding, *platelet concentrates* can be transferred to avoid complications. As bleeding with low *platelet* counts can be life-threatening acute emergencies, immediate action must be taken in these cases. If the *platelet* count is very low, *platelet* concentrates can also be given as a preventive measure. The life span of *platelets* is only a few days. If there is very little or no production of *platelets* in the bone marrow, the administration of *platelet* concentrates may therefore be necessary several times a week.

Platelets carry tissue characteristics (*HLA* markers) that are different for each person. Some patients have *antibodies* against these *HLA* markers. This can happen spontaneously, during illness or after pregnancy. If such *HLA antibodies* are present, the *transfused* blood *platelets* are immediately destroyed and there is not a sufficient increase in *platelets* after a *transfusion* of a *platelet* concentrate. For these patients, special *HLA-compatible platelet* concentrates must be prepared from donors with matching *HLA* characteristics.

The use of *platelet* aggregation inhibitors such as acetylsalicylic acid (ASS) should be considered very carefully, particularly with very low *platelet* counts.

In women who have severe problems with menstrual bleeding, blood loss due to *platelet* deficiency can also be temporarily discontinued with hormone therapy, e.g. continuous administration of contraceptive pills or 3-monthly injections.

3

Activities

In patients with aplastic anaemia, physical activity and exercise are recommended, depending on blood levels and the patient‘s state of health. However, care should be taken to ensure that no excessive demands are made. It is therefore advisable to monitor the pulse rate during exercise. This is particularly important in *anaemia*, because if the red blood cell count is low, the body often tries to compensate for this deficiency by increasing the heart rate, which can lead to excessive strain on the heart. In the case of *thrombocytopenia*, sports with a risk of injury (e.g. martial arts or rock climbing), should be avoided at all costs.

Rehabilitation

If one’s participation in „normal“ life can no longer be carried out as usual due to aplastic anaemia, rehabilitation measures, outpatient physiotherapy or psychological or psychotherapeutic care may be appropriate. These measures should be individually tailored to the patient.

If intensive therapy measures are planned, it makes sense to carry out rehabilitation measures only after these therapies. Physiotherapy or a psychological or psychotherapeutic care is also helpful to accompany the therapy.

If a child suffering from aplastic anaemia is reintegrated after treatment with *immunosuppressive* therapy or transplantation, a family-oriented measure in a paediatric-oncological aftercare facility can be useful due to the high psychosocial burden on the families.

3.6 Prognosis

The higher the *granulocyte* count and the lower the age of the patient at the time of diagnosis, the better the prognosis.

The data on survival after different therapies listed below are statistical data. This means that they cannot be automatically transferred to the individual patient. This list is only intended to give an overview of how possibilities and survival have improved in recent years. There are often subgroups that are not included here. For all specific forms of therapy, the results are significantly better for patients under 20 years of age than for patients over 20. The same applies to patients under 40 years of age compared to patients over 40 years of age. For stem cell transplants, the results are considerably better if the donor provides stem cells directly from the bone marrow and not *peripheral* stem cells obtained from the blood.

According to published data, overall survival in SAA/vSAA is after 3-6 years and separately for the different specific therapies:

- After allogeneic SCT from an *HLA-identical* family donor: 75-90%
- After allogeneic SCT of *HLA-identical* unrelated donors: 65-73 %
- After *ATG/CsA* therapy: 76-96 %

3 3.7 Registry

Patients with evidence of a *PNH clone* can be entered in the international PNH Registry at the University Hospital in Essen in order to extend our knowledge about this group of AA patients.

- **If you are interested or have any questions, please contact**

  Prof. Dr. med. Alexander Röth
  ➔ alexander.roeth@uk-essen.de

Patients with a *telomeropathy* can be included in the telomeropathy registry at the Aachen University Hospital in order to gain further insights into this subgroup of AA patients.

- **If you are interested or have any questions, please contact**

  Prof. Dr. med. Tim H. Brümmendorf
  ➔ tbruemmendorf@ukaachen.de

4

Paroxysmal nocturnal haemoglobinuria (PNH)

- What is PNH?
- Symptoms
- Diagnosis
- Clinical course
- Treatment
- Prognosis
- Wish to have children/pregnancy
- Registry

4 4.1 What is PNH?

4.1.1 General

Paroxysmal nocturnal haemoglobinuria (PNH), like aplastic anaemia (AA), is not *malignant*, but is a very rare, acquired and life-threatening disease. It is due to a defect in the blood-developing stem cells of the bone marrow, and is not inherited.

4.1.2 Occurrence (epidemiology)

The disease frequency (*incidence*) is 1-2 occurrences per million people per year. However, due to the diversity of its symptoms, PNH is rarely recognised and is therefore underdiagnosed. The disease is usually diagnosed in people between the ages of 25 and 45. The frequency of diagnosis is about the same for men and women. There is no familial predisposition.

4.1.3 Origin (pathogenesis)

PNH is caused by a *mutation* (genetic modification) of blood-developing stem cells in the bone marrow. This modification is not present from birth, but only occurs in later life (*somatic* gene *mutation*) and cannot be passed on to children. Healthy and sick cells can be present together at the same time (mosaic).
This gene *mutation* is typically found in a particular section of the genome, the PIG-A gene, and affects one or more types of blood-developing stem cells in the bone marrow. The gene produces an *enzyme* (a biological catalyst) that is

normally required for production of a special anchor system, the *glycosylphosphatidylinositol anchor (GPI anchor)*. This is located on the cell membrane and serves to attach numerous *proteins* to the cell membrane; these *proteins* are involved in regulation of the *immune system*. In this way, they protect the cells from an attack by a certain part of the *immune system*, the '*complement system*', by marking the cells as 'self' or non-foreign.

Two of these proteins play a particularly important role:

- Complement decay accelerating factor (DAF, CD55)
- Protectin (MAC-IP: Membrane attack complex inhibitory protein, and MIRL: Membrane inhibitor of reactive lysis, CD59)

Loss or complete absence of *GPI-anchored proteins* on the cell membrane of *erythrocytes*, *leukocytes* and *platelets* makes these cells more susceptible to destruction by the *complement system*. This leads to a rupture of the *erythrocytes* in the blood vessels (*intravascular haemolysis*) and activation of the *platelets*, which can lead to *thrombosis*.

- **The *complement system* serves to defend the body against infectious agents, parasites, foreign molecules, etc. Once activated, a progressive cascade-like process (*complement cascade*) starts, which can end with destruction of the target cell.**

4

4.2 Symptoms of PNH

4.2.1 Low cell counts (cytopenia)

Anaemia
Destruction of red blood cells (*haemolysis*) can lead to *anaemia* and the loss of oxygen carriers (*haemoglobin*).

Symptoms include:

- Pale skin (non-specific sign)
- Loss of stamina, lack of concentration, depression, *fatigue*, heavy legs and rapid tiredness
- Shortness of breath (*dyspnoea*) under load due to a smaller number of oxygen carriers
- Dizziness, ringing in the ears, increased *heart rate* (*tachycardia*), chest pain (*angina pectoris*), visual disturbances

! ***Anaemia* may be so severe that *transfusion* of red blood cells (*packed RBCs*) becomes necessary.**

Further loss of cell lines
In addition to the red blood cell line, other blood cell lines may be reduced (*cytopenia*), such as *platelets* (*thrombocytopenia*) or *granulocytes* (*neutropenia*).

4.2.2 Effects of haemolysis

Destruction of red blood cells leads to increased levels of bilirubin (a bile pigment) in the blood. This may cause the skin and the *sclera* (white outer layer of the eyeball) to turn yellow. This is also referred to as *jaundice*.
Haemoglobin is also released when the red blood cells break down. If the levels of free *haemoglobin* become excessive, some can be eliminated via the kidney, resulting in dark, red-brown urine (*haemoglobinuria*).
Free *haemoglobin* leads to reduced availability of nitric oxide (NO) via various intermediate steps. Nitric oxide is required for relaxation of smooth muscle (located e.g. in the gastrointestinal tract and lungs); insufficient levels of NO result in increased tension of the smooth muscles, e.g. spasms and constriction of vessels.

This explains many of the clinical symptoms of PNH:

- Severe, often crisis-type abdominal pain
- Cramping of the oesophagus with swallowing disorders (*dysphagia*)
- High blood pressure (*Hypertension*)
- High blood pressure in the lung circulation (*pulmonary hypertension*) with shortness of breath
- Renal insufficiency
- *Erectile dysfunction*

4.2.3 Fatigue

Fatigue is unusually persistent tiredness or exhaustion that may significantly impair physical and mental performance. It is characterised by the fact that increased rest or sleep results in little or no improvement.
Potential causes of *fatigue* are *anaemia* and destruction of red blood cells with the resulting lack of *nitric oxide* (NO), as well as disorders of the *immune system* and/or metabolism.

4.2.4 Thrombosis tendency (thrombophilia)

One of the most dangerous consequences of the lack of nitric oxide is formation of blood clots (*thrombosis*). The *platelets* are presumably activated by the NO deficiency, and this causes abnormal clots. These can occur in various parts of the body, including the liver or brain and both *arteries* and *veins*.
The symptoms and complaints associated with PNH may be permanent. In addition, activation of the *complement system* by infections, pregnancy or stress may lead to further exacerbation of the symptoms, including greatly increased destruction of red blood cells (*haemolytic crisis*). This condition may be life-threatening if not treated. Blood clots can clog the small blood vessels in the kidneys, which can lead to acute kidney failure. There is also an increased risk of *thrombosis* during these *haemolytic crises*. In these situations *packed RBCs* are often required.

4.3 Diagnosis of PNH

Diagnostic tests for PNH

The method used to diagnose PNH is *flow cytometry*. This method is very sensitive and can detect a very small number of cells that have been altered as a result of the disease. In addition, the proportion of affected cells (the *PNH clone* size) and the affected cell types (e.g. *erythrocytes* or *granulocytes*) are determined very accurately. *Venous* (*peripheral* blood) is used for this test.

Additional tests are usually carried out during the initial diagnosis:

- The patient's (and family's) medical history (*anamnesis*) are taken, including a targeted survey of symptoms typical of PNH (see Section 4.2 „Symptoms of PNH")
- Physical examination with regard to the special aspects mentioned above: signs of *anaemia* or *jaundice*, indications of *acute* or previous *thrombosis*, evidence of bleeding, constitutional abnormalities such as congenital aplastic anaemia (see Chapter 3 AA), and enlargement of the spleen (*splenomegaly*)
- Cell investigations
  - Microscopic differential haemogram
  - *Reticulocytes*
- Clinical chemistry
  - *Haemolysis* parameters: in particular *LDH*, haptoglobin, bilirubin
  - Renal function parameters: *creatinine,* urea

- Levels of vitamin B12 and folic acid
- Iron status: *ferritin*, transferrin, transferrin saturation, *reticulocyte haemoglobin*.
  With *ferritin* values > 1000 µg/l, further clarification of possible organ damage due to possible iron overload
- *BNP* (B-type brain natriuretic peptide)) value in the blood serum to assess function of the right heart

- Functional diagnostics
  - Ultrasound of abdomen
  - Lung function
  - ECG

Diagnostic tests of bone marrow with *cytology*, *cytogenetics*, and *histology* should be performed at the time of the initial diagnosis. This is particularly important if there is also *cytopenia* severe enough that PNH in connection with another haematological disease (e.g. aplastic anaemia or myelodysplastic syndrome (MDS)) must be suspected.
With evidence of PNH cells (*PNH clone*) or diagnosis of a *bone marrow insufficiency* syndrome, check-ups should be carried out every 6 months, especially in the first two years after initial diagnosis and in the case of new symptoms. It is important to measure the extent of the *PNH clone* as a proportion of the total number of bone marrow cells. This parameter is useful for estimating the prognosis and managing treatment of the disease.

4.4 Clinical course of PNH

4.4.1 General

The symptoms and handicaps associated with PNH can vary widely and may lead to deterioration of the quality of life. Due to the mechanisms of the disease (mentioned above), *arterial* and *pulmonary hypertension* (high blood pressure in the body and lungs) as well as kidney dysfunction can occur. These problems can lead to permanent damage and require continuous follow-up.

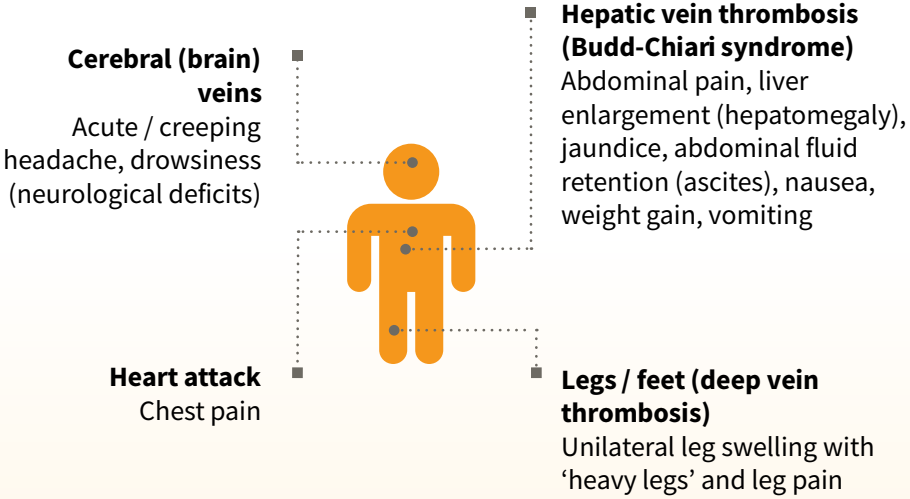
4.4.2 Blood clots (thrombosis/ thromboembolism)

The most feared complication of PNH is formation of blood clots (*thrombosis/thromboembolism*), which can block blood vessels. According to trials, the probability of *thrombosis* occurring without specific PNH therapy was over 30% within 10 years. Approximately 30-50% of all PNH patients develop *thrombosis* in the course of their disease without specific treatment measures. Complications of *thromboembolism* are responsible for up to 67% of all deaths due to PNH. The probability of *thrombosis* may also depend on the number of PNH cells, although even patients with only a few PNH cells have an increased risk of *thrombosis*.

4.4.3 Kidney disease

Two-thirds of all patients with PNH have kidney disease. This is usually due to impairment of the filtering function of the kidney, and therefore its ability to purify the blood plasma.

Thrombosis in PNH patients occurs in several areas, both typical and atypical:



↑ *Figure 6: Occurrence of thrombosis in PNH patients*

The parameter for plasma purification is *creatinine* clearance, which is a measure of how long it takes for *creatinine* (a product of muscle degradation) to be cleared from the blood plasma. The filter function and *creatinine* clearance may both deteriorate during the course of the disease.

4.4.4 Reduced cell numbers (cytopenia)

Significant diminution of blood cell numbers due to concomitant bone marrow disease is the second-most common cause of serious complications (20%). In the course of PNH, approximately 15% of patients develop aplastic anaemia with the absence of all three blood cell lines (*pancytopenia*). Conversely, aplastic anaemia can develop first and be followed by PNH.

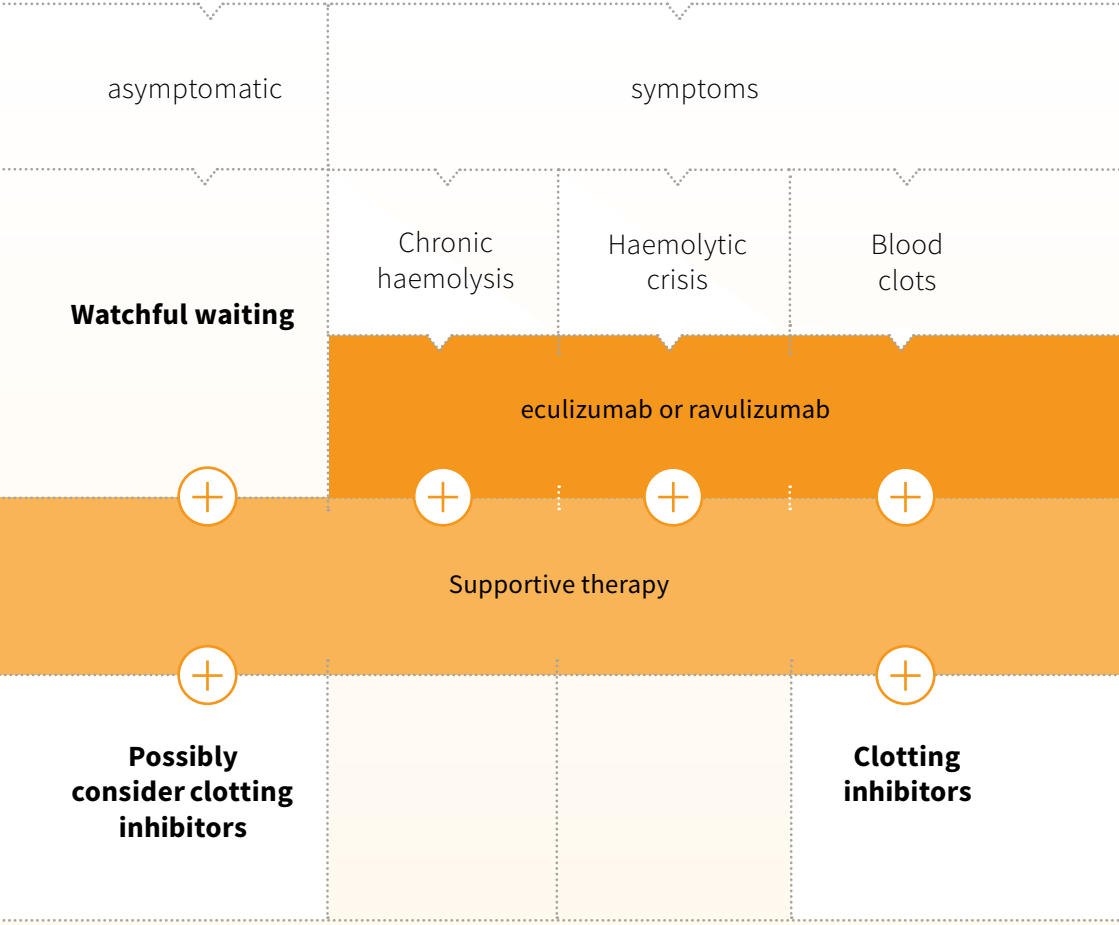
4.5 Treatment of PNH

4.5.1 Overview

How PNH is treated depends on the patient's symptoms. In the absence of relevant symptoms, only detailed check-ups are justified. Supportive measures and medication to inhibit blood clotting (*anticoagulation*), incorrectly referred to as 'blood thinning', may be considered. With symptomatic PNH, the type of treatment depends, among other things, on the severity of blood cell destruction (*haemolysis*) and the presence of blood clots.

4

The following diagram illustrates the treatment concept used for haemolytic PNH

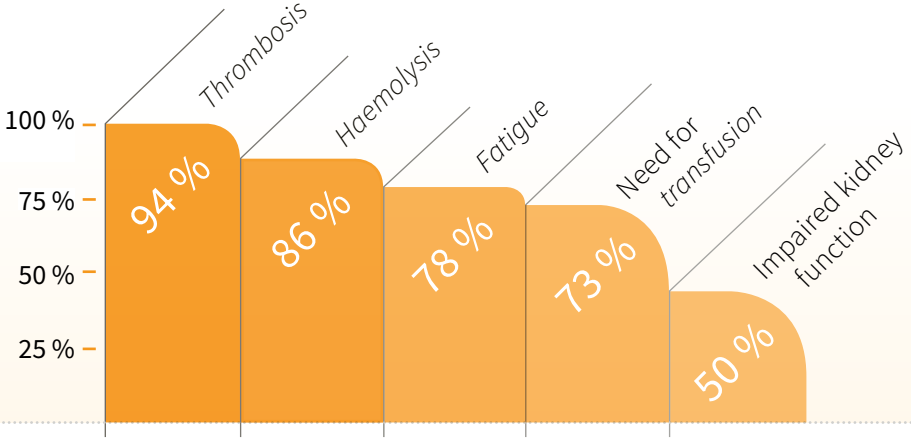


↑ *Figure 7: Simplified presentation of the therapy algorithm. For the complete algorithm, please visit https://www.onkopedia.com/de/onkopedia/guidelines/paroxysmale-naechtliche-haemoglobinurie-pnh/@@guideline/html/index.html*

4.5.2 Specific treatment of PNH

Since the *complement system* (see 4.1.3) attacks the diseased red blood cells, partial inhibition of the system can suppress such destruction.
Since 2007, the only treatment available for PNH therapy has been the eculizumab *antibody*, which must be infused every two weeks. In July 2019, ravulizumab (a development of eculizumab) was authorised in the EU. The new *antibody* is administered as an *infusion* every eight weeks, and according to one trial it is just as effective and compatible as the previous standard therapy.
The following description relates to eculizumab, for which data is available for a much longer timespan. The information on function, precautions and behavioural recommendations is analogous to that for treatment with ravulizumab.
Eculizumab blocks activity of the C5 protein, part of the *complement system*. Various studies have shown that with this blockade, eculizumab greatly reduces the destruction of red blood cells in the blood vessels (*intravascular haemolysis*). There was a significant improvement in the quality of life for PNH patients treated with eculizumab. This improvement was even observed in patients who did not experience normalisation of *haemoglobin* levels. This suggests that, in addition to improving *anaemia*, part of the effect is due to blockage of the blood destruction (*haemolysis*) itself.
As a further consequence of the reduced destruction of the red blood cells, there was a significant decrease in the *transfusion* requirement, *anaemia*, *fatigue*, crisis-type abdominal pain, as well as a reduction in high blood pressure (*arterial hypertension*) and *pulmonary hypertension*. In addition, clinical trials showed improvement or even normalisation of kidney function after a previous renal impairment.

4 Improvement of PNH complications



↑ *Figure 8: Effect of eculizumab with treatment of PNH, Source: 1. Hillmen P et al. NEJM 2006; 355:1233-1243; 2. Schubert J et al. BJH 2008; 142:263-272; 3. Hillmen P et al. Blood 2007, 110:4123-4128; 4. Brodsky A et al. Blood 2008; 111:1840-1847; 5. Hillmen P et al., Am J Hematol 2010;8:553-559; 6. Technical Information Soliris® (eculizumab).*

The aim of treatment is to prevent serious, life-threatening complications and resulting damage to the affected organs. Eculizumab is administered as an *infusion* into a *vein* (*intravenous*) and can be administered on an outpatient basis. The *infusion* is usually given once a week for saturation in the first four weeks, and then every two weeks as maintenance therapy.

Medical reasons for treatment with eculizumab include

- Blood clots
- Crisis-type abdominal pain
- *Haemolytic* crises
- PNH-related impairment of kidney function
- Need for *transfusion*
- *Pulmonary hypertension* associated with PNH

The data from authorisation studies and current evaluations of long-term therapy show that this therapy is very well tolerated. Headaches are a very common side effect at the start of therapy. Infections, changes in blood count, insomnia, gastrointestinal symptoms, skin problems, flu-like symptoms and *fatigue* are among the common side effects.
Due to inhibition of the *complement system*, the body cannot provide sufficient protection against certain bacteria (*meningococci*), which can cause blood poisoning or bacterial meningitis. Vaccination against *meningococcal* disease is therefore absolutely necessary during treatment with eculizumab. Two different vaccines are recommended (Menveo®/Nimenrix® and Bexsero®/Trumenba®) to cover as many of the meningococcal strains as possible (A, C, W135, Y at the start

! **In case of fever (temperature > 38.0°C), rash, strong feeling of illness or neck stiffness, it is crucial that „stand-by therapy“ (e.g. ciprofloxacin 750 mg) is provided as soon as possible and a doctor is consulted immediately to initiate further diagnosis and, if necessary, extended antibiotic therapy. If ciprofloxacin cannot be given, amoxicillin or clavulanic acid 1000 mg are stand-by options.**

of therapy and B during ongoing therapy), although 100% protection is not achieved. Booster vaccinations should be given every three years.

Clinical trials showed that PNH patients complained more of headaches after the initial doses of eculizumab. This is a sign of the effectiveness of the medication. By decreasing the destruction of the red blood cells, more nitric oxide (NO) is available and the blood vessels can expand, but the body needs to get used to this normal condition.

However, eculizumab therapy does not reduce the number of damaged cells or cure the disease. On the contrary, the *antibody* protection means that fewer of the diseased red blood cells disintegrate, so that more of them remain. An increase in the number of these *erythrocytes* is therefore a sign of effective therapy. Adherence to regular treatment intervals (every 14±2 days) is essential to ensure continuous protection of the injured cells and to avoid the complications of PNH (*breakthrough haemolysis*).

Due to the reduced destruction of the damaged red blood cells, little or no *haemoglobin* (and thus iron) is excreted in the urine. Due to the elimination of this *chronic* loss of iron via the kidney, increased iron storage is observed in some PNH patients receiving eculizumab therapy. These patients should therefore be monitored regularly (especially if they have concomitant aplastic anaemia), to ensure that they discontinue any ongoing treatment with iron tablets at an early stage and, if necessary, that they remove excess iron with *chelate therapy.*

Despite the successful suppression of cell destruction in the blood vessels (*intravascular haemolysis*) by eculizumab, a minor degradation of the diseased red blood cells does take place outside the vessels (*extravascular haemolysis*). This can be detected with a special blood test (*Coombs test*).

4.5.3 Symptomatic therapy

In addition to specific treatment of PNH with eculizumab, there are other options for treating the symptoms. Symptoms of *anaemia* can be treated with *packed RBCs*. Although small amounts of *complement* factors are added by *transfusion*, there is no increase in complement-mediated *haemolysis*. This also applies to the use of *platelet* concentrates (see Chapter 3.5.5, blood transfusion).
If affection with PNH is not directly related to bone marrow failure, it is referred to as „classical PNH“. If PNH is not treated, iron deficiency often develops due to the ongoing loss of *haemoglobin* via the kidneys. As iron is necessary for the development of red blood cells, it must be supplemented in such situations. Iron can be administered in the form of tablets or a *venous infusion*. Oral preparations should be taken daily or every other day on an empty stomach. Iron should not be taken simultaneously with antibiotics or medications for neutralising stomach acid (*antacids*). If appropriate iron treatment is started, the decision to take iron supplements must be reviewed regularly. For this purpose, *ferritin* levels should be monitored as part of the regular medical check-ups.
Due to the increased (compensatory) development of red blood cells, there is an increased need for folic acid and possibly vitamin B12. Supplementation should generally be in the form of e.g. 5 mg folic acid per day. Vitamin B12 should be taken according to current levels.
In previous studies, it was found that the risk of *thrombosis* is associated with the quantity of PNH cells and the severity of *haemolytic* activity. The occurrence of *thrombosis* increases significantly if the proportion of GPI-deficient *granulocytes* is more than 50% and/or the *LDH* value is more than 1.5 times

the upper limit. If such patients are given *prophylactic* clotting inhibitors, they develop significantly less *thrombosis*.

The following recommendations therefore apply:

- The use of *anticoagulant* medication should be decided on an individual basis for each patient.
- *Prophylactic* clotting inhibitors are not necessary with eculizumab therapy.
- If *prophylactic* clotting inhibition has been initiated prior to eculizumab therapy, one should consider discontinuing it once *haemolytic* activity has normalised during eculizumab therapy. However, patients should under no circumstances discontinue treatment without consulting their doctor.
- *Anticoagulation* should be applied if *thrombosis* has already occurred. The duration depends on the location of the *thrombosis* and its clinical course.
- In the case of risk situations such as being bed-bound, long-term restriction of movement (plaster cast), surgery or long trips (> 4 hours in a bus or aeroplane), clotting inhibitors should be taken as a *prophylactic* measure according to the current *platelet* values.
- Bacterial infections need to be detected at an early stage and treated appropriately with an antibiotic, since infection can lead to *acute* deterioration of PNH and even a *haemolytic crisis*.
- Adequate fluid intake (*hydration*) should be ensured in the event of a *haemolytic crisis*. Anti-infection therapy, *transfusions* and eculizumab may be required; if the kidneys are endangered, purification (*dialysis*) may be necessary.

- In exceptional cases of concomitant bone marrow disorder (*bone marrow insufficiency*) or after the development of kidney-related (*renal*) *anaemia*, administration of *haematopoietic* (blood-forming) growth factors, e.g. *erythropoietin* or *G-CSF*, may be useful.
- If bone marrow deficiency (*aplasia*) is a greater concern than PNH, *immunosuppressive* therapy, stem cell or bone marrow transplantation should be performed (see Chapter 3.5).

In addition, the current vaccination status should be discussed with the treating haematologist, especially with regard to vaccination against pneumococcal pneumonia and influenza viruses.

4.5.4 Healing of PNH

The only treatment of PNH with the prospect of a cure (*curative* approach) is transplantation of allogeneic bone marrow or stem cells. However, this is accompanied by a significant rate of complications (*morbidity*) and *mortality*. Therefore, the indication (therapeutic decision) for a transplant should be considered very carefully, especially since *antibody* therapy with eculizumab is now an option.

Medical reasons for a stem cell transplant are:

- Recurrent, life-threatening *thromboembolic* complications that do not respond to any other therapy
- Very severe (*refractory*) *haemolytic anaemia* that is not affected by therapy and requires *transfusions*

- Presence of PNH in addition to aplastic anaemia (AA) or myelodysplastic syndrome (MDS), if AA or MDS already justify a transplant
- Transition to aplastic anaemia or myelodysplastic syndrome

4.5.5 Prospects

Several new substances that inhibit the *complement system* are currently being investigated in clinical trials.

4.6 Prognosis

PNH patients now have approximately the same life expectancy as the normal population, since eculizumab therapy significantly reduces the occurrence of *thromboembolic* events.

4.7 Wish to have children/ pregnancy

Until a few years ago, PNH patients were advised not to become pregnant, because life-threatening complications were often observed in the mother and child. This risk has been significantly reduced with *antibody* therapy, so the issue of family planning arises again. Meanwhile, reports of pregnancies during eculizumab treatment are available and show very encouraging results, although the number of cases is limited. These pregnancies were basically without complications, and all the children have been healthy. However, if women wish to become (or already are) pregnant, they should seek support from a specialised centre with haematological and gynaecological expertise in order to clarify the individual risk profile of the patient and, if necessary, to adjust the dose of eculizumab.

4

4.8 Registry

Since PNH is an extremely rare disease, relevant information on the disease and its treatment can only be obtained by analysing the data of as many PNH patients as possible at an international level.
The International PNH Patient Registry was established for this purpose. It documents data on the course of the disease and the quality of life in anonymised form every six months after receiving patient approval. Since new knowledge of the disease and further improvement of the therapy can only be achieved on the basis of such information, as many PNH patients as possible should make their data available to the Registry.

■ **PLEASE HELP!**
If you would like to help or have any questions, please email to

Prof. Dr. med.
Alexander Röth
→ alexander.roeth@uk-essen.de

Prof. Dr. med.
Hubert Schrezenmeier
→ h.schrezenmeier@blutspende.de

Further information on clinical studies can be found in the German brochure „Therapiestudien in der Hämato-Onkologie“ of the German Leukaemia & Lymphoma Aid at

➔ www.leukaemie-hilfe.de/infothek/eigene-publikationen/informationsbroschueren

5 Trials

Only a few treatment options were available a few years ago, but approval studies are now underway for new medications to treat aplastic anaemia and PNH. You can find information about trials on our website → **https://aa-pnh.org/aa-pnh-diseases/clinical-trials/** and with the search function on the following websites:

German Register of Clinical Studies	→ **www.drks.de**
European Medicines Agency, EU Clinical Trials Register	→ **www.clinicaltrialsregister.eu**
National Institutes of Health, U.S. National Library of Medicine	→ **www.clinicaltrials.gov**
World Health Organization, International Clinical Trials Registry Platform	→ **https://trialsearch.who.int/**

6

Specialised centres and doctors

- Germany
- Austria
- Switzerland

6 List of specialised centres & doctors

in Germany, Austria and Switzerland sorted by countries and locations, case numbers and participation in studies

Germany

City	Hospital	Cases of AA: 0-9	Cases of AA: 10+	Cases of PNH: 0-9	Cases of PNH: 10+	Participation in studies	Publications of AA/PNH
Aachen	**Aachen University Hospital** Medical Clinic IV Haematology and Oncology Pauwelsstraße 30 D - 52074 Aachen		✓		✓	✓	
	Prof. Dr. med. Tim H. Brümmendorf Phone: +49 241 80 89805 Fax: +49 241 80 82449 tbruemmendorf@ukaachen.de						✓
	Dr. med. Jens Panse Phone: +49 241 80 89947 Fax: +49 241 80 82449 jpanse@ukaachen.de						✓
	Priv.-Doz. Dr. med. Fabian Beier Phone: +49 241 80 80703 Fax: +49 241 80 82449 fbeier@ukaachen.de						✓

City	Hospital	Cases of AA 0-9	Cases of AA 10+	Cases of PNH 0-9	Cases of PNH 10+	Participation in studies	Publications of AA/PNH
Berlin	**Charité University Hospital, Berlin** CVK: Campus Virchow Hospital Centre for Tumour Medicine CC14 Medical Clinic for Haematology, Oncology and Tumour Immunology Augustenburger Platz 1 D - 13353 Berlin		✓		✓		✓
	Prof. Dr. med. Jörg Westermann Phone: +49 30 450 553 141 Fax: +49 30 450 553 914 joerg.westermann@charite.de						
	Dr. med. Michaela Schwarz Phone: +49 30 450 665 304 Fax: +49 30 450 553 930 michaela.schwarz@charite.de						
Essen	**Essen University Hospital *** Medical Clinic IV Haematology and Oncology Haematology Clinic WEST GERMAN TUMOUR CENTRE Hufelandstraße 55 D - 45147 Essen		✓		✓	✓	
	Prof. Dr. med. Alexander Röth Phone: +49 201 723 5136 Fax: +49 201 723 1716 alexander.roeth@uk-essen.de						✓

*** medical care of more than 50 AA and PNH patients per year**

6

City	Hospital	Cases of AA: 0-9	Cases of AA: 10+	Cases of PNH: 0-9	Cases of PNH: 10+	Participation in studies	Publications of AA/PNH
Hamburg	**Hamburg-Eppendorf University Hospital** Oncology-Haematology Outpatient Clinic, UCCH Martinistraße 52 D - 20246 Hamburg		✓	✓		✓	✓
	Dr. med. Philippe Schafhausen Tel: +49 40 7410 57122 Tel: +49 40 7410 53980 (Ambulanz/outpatient) schafhausen@uke.de						
Hanover	**Hanover Medical School** Internal Medicine Centre Clinic for Haematology, Haemostaseology, Oncology and Stem Cell Transplantation Carl-Neuberg-Straße 1 D - 30625 Hannover		✓	✓			
	Prof. Dr. med. Arnold Ganser Phone: +49 511 532 3020 Fax: +49 511 532 8041 haematologie.onkologie@mh-hannover.de						✓
	Prof. Dr. med. Michael Heuser Phone: +49 511 532 3720 Fax: +49 511 532 8049 heuser.michael@mh-hannover.de						✓

City	Hospital	Cases of AA: 0-9	Cases of AA: 10+	Cases of PNH: 0-9	Cases of PNH: 10+	Participation in studies	Publications of AA/PNH
Riesa	**ELBLAND HOSPITAL Riesa** Haematology, Oncology and Tumour Immunology Weinbergstraße 8 D - 01589 Riesa	✓		✓			✓
		Prof. Dr. med. Jörg Schubert Phone: +49 3525 75 3553 Joerg.Schubert@elblandkliniken.de					
Ulm	**University Hospital Ulm*** Institute of Clinical Transfusion Medicine and Immunogenetics Ulm gGmbH (ICTMI) Institute of Transfusion Medicine, University Hospital Ulm Helmholtzstraße 10 D - 89081 Ulm		✓		✓	✓	
		Prof. Dr. med. Hubert Schrezenmeier Phone: +49 731 150 550 Fax: +49 731 150 500 h.schrezenmeier@blutspende.de					✓
		Dr. med. Britta Höchsmann Fax: +49 731 150500 b.hoechsmann@blutspende.de					✓

*** medical care of more than 50 AA and PNH patients per year**

6 Austria

City	Hospital	Cases of AA 0-9	Cases of AA 10+	Cases of PNH 0-9	Cases of PNH 10+	Participation in studies	Publications of AA/PNH
Linz	**Ordensklinikum Linz** Elisabethinen Hospital Linz GmbH Department of Internal Medicine I Haematology with Stem Cell Transplantation, Haemostaseology and Medical Oncology Fadingerstraße 1 A - 4020 Linz	✓		✓		✓	
	Dr. med. Sigrid Machherndl-Spandl Phone: +43 732 7676 4434 Fax: +43 732 7676 4416 E-Mail: sigrid.machherndl-spandl@ordensklinikum.at						
Vienna	**Allgemeines Krankenhaus Wien** University Clinic for Internal Medicine 1 Clinical Department of Haematology and Haemostasis Währinger Gürtel 18-20 A - 1090 Vienna	k.A.				✓	✓
	Univ.-Prof. Dr. med. Wolfgang Füreder Phone: +43 1 40400 44690 (Tagesklinik/outpatient) Fax: +43 1 40400 40300 wolfgang.fuereder@meduniwien.ac.at						

SWITZERLAND

City	Hospital	Cases of AA 0-9	Cases of AA 10+	Cases of PNH 0-9	Cases of PNH 10+	Participation in studies	Publications of AA/PNH
Basel	**Basel University Hospital (USB)**		✓	✓		✓	
	Centre for Stem Cell Transplantation Haematology Clinic Petersgraben 4 CH - 4031 Basel						✓
							✓
	University Children's Hospital beider Basel (UKBB)	✓		✓		✓	
	Oncology/Haematology Spitalstrasse 33 CH - 4056 Basel						✓
Zurich	**University Hospital Zurich (USZ)**						
	Medical Oncology and Haematology Clinic Rämistrasse 100 CH - 8091 Zurich						
	Zurich Univ. Children's Hospital (UZH)	✓		✓		✓	
	Paediatric Haematology/ Oncology FMH, FAMH Steinwiesstrasse 75 CH - 8032 Zurich						

Prof. Dr. med. Jakob Passweg
Phone: +41 61 265 4254
Jakob.Passweg@usb.ch

Dr. med. Beatrice Drexler
Phone: +41 61 328 6675
Beatrice.Drexler@usb.ch

Prof. Dr. med. Thomas Kühne
Tel.: +41 61 704 1212
Fax: +41 61 704 1213
thomas.kuehne@ukbb.ch

PD Dr. med. Urs Schanz
Phone: +41 44 255 3758
Fax: +41 44 255 4568
urs.schanz@usz.ch

PD Dr. med.
Markus Schmugge Liner
Phone: +41 44 266 7307
Fax: +41 44 266 7171
markus.schmugge@kispi.uzh.ch

7

Personal experiences

- by Michael Kaiser
- by Ulrike Göbel

Personal experiences

By Michael Kaiser

When I was diagnosed with the disease (August 1984), I was just over 18 years old. Growing up was totally different from what I expected.
My admission to the clinic was quite dramatic, because I was already very weak and had lost so much blood due to a dental treatment that the doctors were initially occupied by keeping me alive for a few days before they could establish a diagnosis. The following weeks at the clinic were a huge psychological burden for myself and my parents.
In November 1984, I received the first ATG therapy (rabbit serum), which was not successful. In February 1985 I had the second ATG treatment; this time with horse serum, and I was lucky: the values improved slowly and I was able to start an apprenticeship in September. The treatment was done without any immunosuppressants, but with high doses of cortisone. The values stabilised over the years to the point where I could live a „normal“ life. I got married, had two children, got a good job (and spent too much time at work!).
In 1995 the values started to get worse, so that in May 1997 I had to go back to the clinic where I had my third ATG treatment, this time with Sandimmun®. After about six months I went back to work, but the values never recovered or stabilised properly.

In October 2000, after some private problems (including separation and divorce) I had a further relapse, which hit me very hard. I was poorly stabilised by the transfusions and treated a few times with Sandimmun®, but without success.

It was hard to know what to do. A fourth ATG therapy seemed to be too risky and unpromising, while a transplant looked pointless and even dangerous, given my history and the fact that only a an unrelated donor would have been eligible.

As my condition continued to deteriorate, the doctors and I jointly decided for a bone marrow transplantation (BMT). I was very lucky, as a suitable donor was soon found and a date for the BMT was set. I was admitted to hospital on 25.10.2001, received new stem cells on 09.11.2001 and was released from hospital on 30.12.2001. My time in the clinic and afterwards was very difficult and intense, but now I'm doing really well. Particularly after leaving hospital, it was very important for me to search for and find my own way, and that gave me back something like an everyday life. The regulations and restrictions following the BMT were very burdensome, but necessary. However, I couldn't manage everything perfectly, since I lived by myself and could hardly get help from others.

Since my last relapse in October 2000 I have had almost no infections or other problems. I think this is because, although I was still weak, I was mostly out in the open and getting plenty of exercise, and I was treated by a very good homeopath. I'm convinced that homeopathy, in addition to the outstanding achievements of conventional medicine (special thanks to Ms. Waterhouse at the München-Schwabing Hospital and Mr. Kolb at the Grosshadern Hospital), as well as my own efforts and my positive attitude, have made a significant contribution to my being able to live with severe aplastic anaemia for so long and that I could recover so quickly (and sustainably) after the BMT.

Since early March 2002, I have not taken any medication, my values have improved greatly and I've been stable for over 15 years.

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I received a disability pension from April 2002 to September 2002, and from 01.10.2002, less than a year after the transplant, I was able to return to work in business. I was initially employed for 30 hours a week.
My wish to pass on my experience to others and reorient my private professional life became stronger and stronger.
My next step was to train as a „Teacher for exercise, body awareness and fitness“ and I gave part-time courses in this area. In 2008, I finally took a big step and became an alternative practitioner of psychotherapy. I now work for 20 hours a week as a board member at MFM Deutschland e.V. and work as an alternative practitioner in psychotherapy, lecturer and Qigong teacher.

In my private life I found my great love and became a father for the third time, even though the doctors had said I was infertile due to the transplant.
What was important in all stages of my illness was that I always grasped my opportunities and continued to fight in spite of all the disappointments and setbacks. I'm convinced that you can always find a way if you believe in yourself and don't give up, even if you seem to have hit rock bottom.
I wish all the best to patients with AA and hope that they too will find a way with the help of their doctors to live with the disease and perhaps be cured.
Anyone who is interested is welcome to contact me or read my story in my autobiography „Something old, something new".

August 2020

You can contact me by: ➔ **kaiser.dachau@arcor.de**

7

By Ulrike Göbel

The first abnormalities in my blood count were found in March 1999 in the form of thrombocytopenia, when I went to donate blood (irony of fate?). At that stage I hadn't noticed any physical symptoms such as an increased bleeding tendency. But a few weeks later, the erythrocyte and leukocyte values had changed too; I became anaemic, and there were more lymphocytes than usual among the leukocytes. At first there was no clear diagnosis from the two bone marrow punctures, so that immunosuppressive treatment was prescribed with little justification until October 1999, when another puncture supported the diagnosis of „very severe aplastic anaemia (vSAA)".

By that time I was already dependent on transfusions, and was told to go to hospital as soon as the diagnosis was made, in order to receive the first ATG and begin ciclosporin therapy, which continued until the summer of 2007. The rabbit ATG had no effect, but I continued to receive transfusions (platelets about every 6 days and red blood cells about every 14 days) as well as numerous preventive measures to support my weak immune system. I could only wait and hope that the bone marrow would recover.

In February 2000 I was diagnosed with PNH, but it didn't play a role since treatment of aplastic anaemia was still the focus. Two months later, I received the second treatment with ATG (horse). In June 2000, two months after my therapy, the bone

marrow started to show some platelet production. This was enough to discontinue the transfusions, and *prophylaxis* against infection was gradually tapered off. I received my last foreign RBCs in January 2001, and the first visible PNH crisis occurred at the same time.

By 2002, my blood levels had gradually stabilised, but the haemoglobin levels already showed persistent PNH crises. The associated symptoms were mitigated by regular administration of packed RBCs (since autumn 2005) and prednisolone, but they have significantly impaired my quality of life. I was particularly burdened by a pronounced feeling of weakness, which was often associated with the feeling that a rock was lying on my stomach. I therefore started therapy with the antibody eculizumab in June 2010. Since then, the haemoglobinuria has disappeared; this is a great relief, as I notice the PNH symptoms less often and less intensely. However, I still need transfusions and my stamina is very limited. My leukocyte and platelet values are stable.
I have been on an invalidity pension since 2000. I took advantage of the associated financial security and „leisure time“, and from 2001 to 2006 I studied history part-time at an English online university, which I had always wanted to do. I enjoyed my studies a lot, but the pressure on performance put me under considerable stress and showed me that I cannot really work in a concentrated way in the long term.
My employer has supported me for the entire period of my illness and has employed me for two half days a week since 2001. This gives me the opportunity to take part in professional life and to maintain social contacts in addition to my voluntary commitment. I greatly appreciate this.
The approval of ravulizumab in July 2019 made it possible for me to increase the intervals between attending a practice

or clinic for infusions from every two weeks to every eight weeks. However, the fatigue still makes things difficult, even though my RBC values have now stabilised and I hardly need any concentrates. I have high hopes for medications that are more effective than C5 inhibitors in reducing haemolysis, and some of these are already undergoing clinical trials.

August 2020

You can contact me by email: ➔ **ug-sh@web.de**

8 Glossar

Acute	Sudden onset, rapidly progressing
Aetiology	Cause of a disease
Anaemia	Reduction of red blood cells or their content of (blood pigment); as a result of blood loss, reduced *haemoglobin* production, reduced blood cell development due to bone marrow diseases, increased blood cell decay due to poisoning and metabolic disorders. Anaemia leads to reduced physical capacity.
Anaemia, haemolytic	Form of *anaemia* caused by increased breakdown or decay of red blood cells. This leads to shortening of the life span of the *erythrocytes*. Depending on the site affected, a distinction can be made between *haemolysis* inside the blood vessels (*intravascular*) and outside the blood vessels (*extravascular*).
Anamnesis	Medical history, development of symptoms
Angina pectoris	Sudden pain/tightness in the chest, due to a temporary perfusion disorder of the heart associated with coronary *artery* disease
Antacid	Medication for neutralising stomach acid
Antibody	A *protein* normally produced by the *immune system* to defend against a pathogen that has entered the body or another threat; an antibody binds specifically to certain surface structures of the intruder, and triggers a series of further immune reactions that ultimately lead to the killing and elimination of the pathogen.

Anticoagulation / anticoagulant	Inhibition of blood clotting
Antithymocyte globulin / Anti-T cell globulin	ATG; *immunosuppressive* mixture of *antibodies* obtained from rabbits or horses. It reduces the number of *lymphocytes* (lymphocytopenia), mainly by suppressing circulating T *lymphocytes*. It is used for instance to treat aplastic anaemia and for the *prophylaxis* and therapy of *GvHD* in the context of stem cell transplantation.
Apheresis	Targeted removal of certain components from the blood using a special apparatus
Aplasia / aplastic	Condition of the non-functional bone marrow that cannot develop blood cells
Arterial hypertension	see *Hypertension (arterial)*
Artery / arterial	Blood vessel that carries blood from the heart (exception: coronary arteries) and in which oxygen-rich blood is transported (exception: pulmonary artery)
ATG	see Antithymocyte globulin
Bicytopenia	Lack of blood cells in two cell lines
BNP	Brain (Ventricular) Natriuretic Peptide; hormone produced in the heart that stimulates the kidneys to excrete sodium and fluids
Bone marrow aspiration	Suction of cells and marrow fragments from the bone marrow (usually from the iliac crest) with a hollow needle

Bone marrow biopsy	Taking a sample from the bone marrow (usually from the iliac crest) with a tissue punch. This method enables more precise examinations to be carried out than with *bone marrow aspiration*, since the bone punch cylinder is also obtained.
Bone marrow hyperplasia	Bone marrow with too many cells
Bone marrow hypoplasia	Bone marrow with too few cells
Bone marrow insufficiency	Reduced production of blood cells in the bone marrow
Bone marrow puncture	Piercing through the bone into the bone marrow with a hollow needle in order to remove tissue for examination. Usually performed at the iliac crest, it can be used for *bone marrow aspiration* or *bone marrow biopsy*.
Breakthrough haemolysis	Severe haemolysis with severe symptoms; requires treatment
Cellularity	Cell content of a bone marrow smear
Chelate/chelation therapy	Therapy for removal of excess iron, which was stored e.g. by increased *transfusions* of *packed RBCs*
chronic	Over a long period of time and persistent

Ciclosporin	Also known as cyclosporin A, CsA; *immunosuppressive* medication administered e.g. to treat aplastic anaemia and prevent *GvHD* disease. In high doses and with long-term administration, its main side effects are *hypertension*, tremor of the hands and deterioration of kidney function. Blood levels of CsA must be measured regularly in order to minimise toxic side effects.
Clone	A set of cells that all originate from a single parent cell and that all have the same characteristics
CMV	CMV see *Cytomegalovirus*
Complement cascade	Once the complement system has been activated, a cascade-like process takes place for immune defence
Complement system	A group of plasma *proteins* for immune defence against microorganisms
Complete remission	see *Remission, complete*
Conditioning	Preparation of a patient for stem cell transplantation in the form of high-dose chemotherapy (high-dose therapy) and, if necessary, whole-body radiation. The recipient‘s *immune system* must be suppressed to such an extent that the donor‘s transplant can grow without the risk of rejection.
Contraindication	Reason for not carrying out a treatment
Coombs test	Test for the detection of certain *antibodies* against red blood cells
CR	see *Remission, complete*

Creatinine	Nitrogenous metabolic end product that is excreted via the kidneys. An elevated creatinine level in the blood indicates impaired kidney function
Crisis, haemolytic	Sudden massive *haemolysis*. Possible signs are fever, chills, circulatory problems up to and including collapse, abdominal pain, backache, headache, dark urine and later yellowing of the skin.
CsA	see *Ciclosporin*
Curative	Healing, focused on healing
Cytogenetics / cytogenetic	A branch of genetics in which the number and structure of the chromosomes of a dividing cell are examined under a microscope
Cytology / cytological	The field of general biology that covers the structure and function of cells
Cytomegalovirus	CMV; virus of the herpes group, which can cause serious complications in organ transplanted and immunocompromised patients. The pathogen is widespread in the population. The virus remains in the body for life after initial infection and can be reactivated if the *immune system* is weakened.
Cytopenia	Reduction in the number of cells in the blood, e.g. e*rythro-, leuko-*, granulo-, lympho- or *thrombocytopenia*
Dehydration	Lack of fluid in the body
Dialysis	Blood purification in case of reduced or failed kidney function

Diamond-Blackfan anaemia	also known as *Diamond-Blackfan* syndrome, DBA; severe chronic *anaemia*, usually occurring in early childhood
Differential blood count	Routine examination that indicates the cellular composition of the white blood cells (*leukocytes*) in the blood. The percentages of the individual blood cell types are determined by microscopic counting of a blood smear. The white cells of normal blood include granulocytes (*neutrophils*, eosinophils, basophils), *lymphocytes* and monocytes. The differential blood count plays an important role in the diagnosis of blood diseases, but also infections and inflammations. The determination of the differential blood count is necessary, among other things, to clarify *leukocytopenia* or leukocytosis.
Dysfunction, erectile	Sexual dysfunction in which the penis does not erect or does not erect for long enough
Dysphagia	Problems with swallowing
Dysplasia / dysplastic	Malformation. Degenerated cells are „dysplastic“, i.e. malformed. Dysplastic cells do not mature (differentiate) normally.
Dyspnoea	Shortness of breath
Enzyme	Biocatalyst; a *protein* that mediates all chemical transformations that occur in living organisms (metabolism). The cells of an organism have a specific enzyme for nearly every chemical reaction.

Epidemiology	study of the frequency and distribution of diseases in populations
Erectile dysfunction	see *Dysfunction, erectile*
Erythrocyte / Ery	Red blood cell; erythrocytes make up the majority of cellular blood components. They are formed in the bone marrow, contain *haemoglobin* (the red pigment in blood) and have a life expectancy of about 120 days in healthy people. The *haemoglobin* content of the blood is an important measurement that provides information on e.g. whether a patient is *anaemic*. The function of *haemoglobin* (and therefore the erythrocytes) is to transport oxygen, which is taken up in the lungs, and carbon dioxide, which is released by the lungs.
Erythrocytopenia	Red blood cell (*erythrocyte*) deficiency
Erythropoietin / Epo	A hormone formed in the kidney, which can also be produced by genetic engineering and is available as a medication that stimulates the formation of red blood cells. This substance is administered in certain forms of blood deficiency.
Extravascular	Outside the blood vessels
Fanconi anaemia	Hereditary disease in which red and white blood cells are produced in a reduced quantity and broken down more quickly
Fatigue	Severe tiredness, exhaustion or increased need for rest; a symptom that often accompanies various chronic diseases

Ferritin	*Protein* that stores iron; if *packed RBCs* are given frequently, the ferritin level should be monitored in case *chelation therapy* becomes necessary.
Fibrosis	Abnormal proliferation of connective tissue in the bone marrow or an organ
First-line therapy / first-line treatment	First-choice therapy, may be described in a guideline as the most suitable treatment
Flow cytometry / flow cytometric	Measurement method that enables the analysis of cells that each pass an electric voltage or a light beam at high speed. Depending on the shape, structure and/or colouring of the cells, different effects are produced, from which the properties of the cells can be recorded. Used in the diagnosis of PNH
G-CSF	see *Granulocyte colony stimulating factor*
Gingival hyperplasia	Overproliferation of the gums; may occur with administration of *ciclosporin*
Glycosylphosphatidylinositol anchor	GPI anchor; attaches *proteins* to the cell membrane; the *proteins* CD55 and CD59 protect e.g. the red blood cells from premature decay
GPI anchors	see *Glycosylphosphatidylinositol anchors*

Graft versus host disease	GvHD; graft versus recipient response. The donor's *immune system* transplanted with a foreign donation (e.g. stem cells) can recognise the recipient's body cells as foreign and attack them. A distinction is made between *acute* GvHD (grades 1-4) and *chronic* GvHD (limited and extensive form). The *acute* form is observed in the first 2-3 months after transplantation, later the *chronic* form. The *chronic* form often develops from the *acute* form, but it can also occur anew. Symptoms can be: reddening of the skin, itching, peeling of the skin, inflammation of the mucous membranes, *jaundice*, diarrhoea, abdominal pain, organ failure. *Immunosuppressive* medications are administered for therapy (including *ciclosporin*, *ATG*, cortisone).
Granulocyte	Subgroup of white blood cells; they destroy invading bacteria that can cause diseases
Granulocyte colony stimulating factor	G-CSF; genetically engineered drug that promotes the development of *granulocytes* and leads to washout of stem cells from the bone marrow into the blood. It is tolerated quite well, but may cause temporary fever and limb pain in a small proportion of patients.
Granulocyte, neutrophilic	Subgroup of *granulocytes* with an important role in defending against bacterial and fungal infections
GvHD	see *Graft versus host disease*

Haematoma	Bruise
Haematopoiesis / haematopoietic	Blood development
Haemoglobin	Hb; red blood cell pigment consisting of haem (an iron-containing component) and globin (a *protein*). Binds, transports and releases oxygen and carbon dioxide. Reference values: women 12-16 g/dl or 7.5-9.9 mmol/l, men 14-18 g/dl or 8.7-11.2 mmol/l
Haemoglobinuria	Excretion of *haemoglobin* in the urine, resulting in darkened urine; may lead to acute kidney failure if severe
Haemolysis / haemolytic	Breakdown of red blood cells
Haemolysis, extravascular	Breakdown of red blood cells outside blood vessels
Haemolysis, intravascular	Breakdown of red blood cells inside the blood vessels
Haemolytic anaemia	see *Anaemia, haemolytic*
Haemolytic crisis	see *Crisis, haemolytic*
Hb	see *Haemoglobin*
Histology	Science of tissues: the branch of medicine that involves tissues at the microscopic level
HLA	see *Human leucocyte antigens*
HLA compatibility	Since an unrelated donor can never be completely „identical“, we refer to HLA-compatibility in this context
HLA identity	Complete identity of the 10 most important *HLA* antigens (A, B, C, DRB1, DQB1)

HLA system	An important regulatory system for the organism's immune defences. *HLA typing* is extremely important in preparation for allogenic transplantation. The more similar the HLA systems of donor and recipient, the lower the risk of transplant rejection and *GvHD* and the greater the chance of successful allogeneic stem cell transplantation.
HLA typing	Examination of *HLA* characteristics A, B, C, DRB1 and DQB1 for stem cell transplantation
Human Leucocyte Antigens	HLA system; human *leucocyte* antigen; *protein* structure on the surface of most body cells. They help the *immune system* to differentiate between „self" and „foreign" material.
Hydration	Therapeutic replacement of body fluid deficiency, e.g. in cases of high blood loss or massive diarrhoea. In order to compensate quickly for fluid loss, supplementation is usually carried out as an *infusion*.
Hypertension (arterial)	Arterial hypertension. A clinical picture in which blood pressure in the arterial system is *chronically* elevated. A systolic blood pressure of more than 140 mmHg and/or a diastolic blood pressure of more than 90 mmHg is regarded as hypertension. Temporary increases in blood pressure due to illness, medication, pregnancy or physical exertion are not included in this definition.

Hypertension (pulmonary)	Pulmonary hypertension. A disease characterised by an increase in blood pressure in the pulmonary circulation and often by an increasing rise in vascular resistance in the pulmonary *arteries*. Patients suffer from severely restricted physical performance, circulatory disorders and *fatigue*.
Hypoplasia / hypoplastic	Mal/underdevelopment of the bone marrow or an organ
i.v.	see *intravenous*
Idiopathic	Without identifiable cause
Immune system	Defence system; system that enables the body to fight off infections and to distinguish between its own and foreign tissues. In humans, the immune system consists of specialised *proteins* (antibodies), immune cells (white blood cells) and immune organs. It is responsible for our body's defences against infection.
Immunosuppression / immunosuppressive	Suppression of the *immune system*
Incidence	Frequency of new cases per 100,000 inhabitants per year
Indication	Reason to perform a medical procedure
Infusion	Injection of a liquid into a *vein*
Intravascular	Inside blood vessels
intravenous	i.v.; injection of a medication into a *vein*
Jamshidi needle	Punch needle for *bone marrow biopsy*
Jaundice	Icterus; yellowish discolouration of the skin and mucous membranes

Lactate dehydrogenase	LDH; marker in the blood indicating cell damage
LDH	see *Lactate dehydrogenase*
Leukocyte, leuko	White blood cell. Cells with a wide variety of forms and functions. The leukocytes are responsible for defending against pathogens and removing debris due to decaying cells.
Leukocytopenia	Deficiency of white blood cells
Lymphocyte	Subgroup of white blood cells that play a role in the defence against diseases and foreign substances
Malignant	Characterises abnormal cell growth
Meningococci	Bacteria that colonise the nasopharynx and can lead to serious diseases, e.g. meningitis. They are transmitted from person to person by droplet infection, for example when coughing, sneezing or kissing. There are 13 known meningococcal groups (A, B, C, D, 29E, H, I, K, L, W-135, X, Y and Z). In Germany, group B is the most frequently detected group of meningococcal infections. Infants/babies are most often affected. Early antibiotic therapy is crucial because the death rate is up to 10%. Vaccination is possible against meningococcus groups A, B, C, W-135 and Y.
Monotherapy	Medication with only one active substance
Morbidity	Frequency of illness; complaints and complications caused by an illness or during therapy

Mortality	Death rate
Mutation	Alteration of genetic material (gene)
Neutropenia	Deficiency of *neutrophils*
Neutrophil	see *Granulocyte*, *neutrophilic*
packed RBCs	see *Red blood cell concentrate*
Pancytopenia	see *Tricytopenia*
Partial remission	see *Remission, partial*
Pathogenesis	Origin and development of a disease
Periphery / peripheral	Area outside a centre or origin; peripheral blood is blood in the peripheral circulation
Petechia	pl. Petechiae; tiny, localised, red spot on the skin caused by bleeding from small blood vessels close to the skin. Petechiae are often caused by a lack of *platelets*.
Platelet concentrate	blood with concentrated *platelets* from a blood donor
Platelet / thrombocyte	Smallest form of blood cells, whose main task is to maintain blood clotting
PNH clone	All blood cells affected by the mutation typical of PNH; the size of the PNH clone is a measure of the severity of the disease
PR	see Remission, partial
Progression	Progression of a disease
Prophylaxis / prophylactic	Prevention or precaution
Protein	Macromolecule consisting of one or more long chains of amino acids
Pulmonary hypertension	see *Hypertension, pulmonary*

Recurrence	Relapse; Recurrence of disease after a period without symptoms or complaints
Red blood cell concentrate / RBC concentrate	packed RBCs; blood with concentrated red blood cells (*erythrocytes*), which are collected from donors
Refractory	A disease is refractory if it does not respond to therapy.
Remission	Temporary alleviation or cessation of the symptoms of a disease, but which may not result in a cure. A distinction is made between *complete* and *partial remission*.
Remission, complete	CR (complete remission); complete regression of disease symptoms
Remission, partial	PR (partial remission); decrease in disease symptoms by at least 50%
Renal	Involving the kidney
Reticulocyte	Young, immature red blood cell; precursor of *erythrocyte*
Sclera	White outer layer of the eyeball that surrounds and protects it.
Second-line therapy/ second-line treatment	Treatment according to a guideline after failure (or intolerance) of *first-line treatment*
Somatic	Involving the body
Sonography	Ultrasound; imaging method of examination
Splenomegaly	Enlargement of the spleen e.g. in leukaemia and lymphoma, infection with bacteria or viruses, rheumatic disease, (lysosomal) storage disease. An enlarged spleen may store blood cells and cause a general lack of blood cells (*pancytopenia*). The underlying disease needs to be treated, and in rare cases the enlarged spleen must be surgically removed.

Tachycardia	Accelerated heartbeat (over 100 beats per minute in adults)
Telomere	End of chromosomes that shorten with each cell division
Telomeropathy	Disease in which telomere shortening is exacerbated
Thorax	Chest
Thrombocytopenia	Platelet deficiency
Thrombocyte	A blood clot that is carried into the bloodstream and leads to closure of the affected blood vessel, which is then unable to supply the corresponding organs
Thrombophilia	Condition in which an imbalance of clotting factors increases the risk of *thrombosis* (developing blood clots)
Thrombopoietin	Hormone that stimulates *platelet* formation
Thrombosis	Vascular disease in which a clot forms in a blood vessel; can occur in any vessel, most commonly in *veins*, especially in the deep *veins* of the legs
Transfusion / transfuse	Transfer of blood or blood components
Tremor	Shaking
Tricytopenia	*Pancytopenia*; deficiency of blood cells of all three cell lines (*erythrocytes, leukocytes, platelets*)
Vein	Blood vessel that leads to the heart and transports oxygen-poor blood (exception: pulmonary vein)

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APLASTISCHE
ANÄMIE & PNH e.V.

Aplastische Anämie & PNH e.V.
Postfach / P.O. Box 52 03 25
12593 Berlin
Germany
+49 30 54909 4080
+49 30 54909 4089
info@aa-pnh.org
www.aa-pnh.org

Bank details:
IBAN: DE97 7005 4306 0055 1186 99
BIC: BYLA DE M1 WOR
Sparkasse Bad Tölz-Wolfratshausen

www.aa-pnh.org