UNDERSTANDING
SEVERE CHRONIC NEUTROPENIA

A handbook for patients and their families

Written for the

Severe Chronic Neutropenia International Registry

2. Revised edition 2017

Cornelia Zeidler, M.D., MPH

Severe Chronic Neutropenia International Registry
Hannover Medical School
Carl-Neuberg-Straße 1
D-30623 Hannover, Germany
First edition from November 2000, written by:

Audrey Anna Bolyard, R.N., B.S.
Tammy Cottle
Carole Edwards, R.G.N/R.S.C.N., BSc.
Sally Kinsey, M.D.
Beate Schwinzer, Ph.D.
Cornelia Zeidler, M.D.
CONTENTS

Preface .............................................................................................................................................. 5
Introduction ...................................................................................................................................... 6
   How the blood is formed .............................................................................................................. 7
   What is Neutropenia? ................................................................................................................... 9
      Symptoms of Neutropenia ...................................................................................................... 11
      Causes of Neutropenia .......................................................................................................... 12
         Incidence of severe chronic Neutropenia ........................................................................... 12
      Basic information on heredity ............................................................................................... 13
         Genetics of congenital Neutropenia ................................................................................... 13
      Types of Severe Chronic Neutropenia .................................................................................. 15
         Severe Congenital Neutropenia ........................................................................................ 16
         Cyclic Neutropenia .............................................................................................................. 18
         Shwachman-Diamond Syndrome (SDS) ............................................................................ 20
         Metabolic Disorders with Neutropenia .............................................................................. 21
            G6PC3-CN ....................................................................................................................... 21
         Idiopathic Neutropenia ...................................................................................................... 22
         Autoimmune Neutropenia ................................................................................................. 22
         Neonatal Alloimmuneneutropenia (NIN) ........................................................................... 24
         Other Conditions Associated with Neutropenia .................................................................. 24
      Diagnostic Tests Used in Severe Chronic Neutropenia ................................................................. 26
         Blood Count Monitoring .................................................................................................... 26
         Other Blood Tests .............................................................................................................. 26
         Detection of Antibodies ..................................................................................................... 26
         Molecular genetic analysis ................................................................................................. 27
         Bone Marrow Aspiration/Biopsy .......................................................................................... 27
            Samples of the Bone Marrow (Morphology) ................................................................. 28
         Cytogenetic Evaluation and Molecular Testing .................................................................... 29
         Analysis of the G-CSF Receptor Gene ............................................................................... 29
         Investigations in Patients with Other Conditions .................................................................. 30
      Treatment of Subtypes of Severe Chronic Neutropenia ................................................................. 30
Granulocyte-Colony Stimulating Factor (G-CSF) ......................................................... 32
Hematopoietic Stem Cell Transplantation ................................................................. 34
Other Treatments ..................................................................................................... 35
Supportive Treatment ............................................................................................. 36
Prognosis .................................................................................................................. 38
Secondary Leukemia ................................................................................................. 38
Long-term Management and Monitoring of Severe Chronic Neutropenia .......... 39
  ANC Monitoring .................................................................................................... 40
  Bone Marrow Monitoring ...................................................................................... 40
  Periodontitis .......................................................................................................... 40
  Pregnancy ................................................................................................................ 41
  Psychosocial Issues ............................................................................................... 41
  Patient support groups ......................................................................................... 42
Severe Chronic Neutropenia International Registry ............................................ 45
  The European Branch of the SCNIR ................................................................. 46
  Support Groups .................................................................................................... 48
Frequently Asked Questions and Answers on Severe Chronic Neutropenia .... 50
Glossary .................................................................................................................... 59
Dear readers,
Research in the field of severe chronic Neutropenia is in a phase of rapid development. During the past fifteen years knowledge on this kind of disease has multiplied thanks to intensive fundamental research work. Therefore, we had to revise, update and expand the content in this second edition to include the latest information in this field. Most of the changes concern the knowledge on new molecular genetics, the causative mutations of genes, but also disease related symptoms and long-term consequences.

We want to give the most up-to-date information to you and hope to be able to answer all your upcoming questions.

Cornelia Zeidler, M. D., MPH
Introduction

Severe chronic neutropenia (SCN) is the name given to a group of conditions in which neutropenia is the primary or a major problem in association with other clinical features. The severity and symptoms of neutropenia differ widely among the various sub-types of neutropenia and even from patient to patient within each disease type.

This handbook is designed to give you a better understanding of SCN. It has been written to answer many of the questions you may have about neutropenia and treatment. We hope it helps you and/or your child in coping with the disease. The purpose of this document is to give you information and to empower you to ask questions to your physician. Learning about neutropenia, its causes and best treatments, is an ongoing process. Research is continually adding to what we know and recommend to patients with neutropenia and their families. Consequently, this handbook is not all-inclusive.

You can obtain up-to-date information about neutropenia through websites sponsored by the Severe Chronic Neutropenia International Registry (termed “SCNIR” or “Registry” in this document):

- www.scnir.de;
- www.depts.washington.edu/registry/

and the Parent/Patient support group National Neutropenia Network (NNN):

- www.neutropenianet.org/

or through reading research papers available at Pubmed:

The staff and Advisory Board members of the SCNIR wrote the first edition of this handbook. The SCNIR was established in 1994 under the sponsorship of Amgen Inc., Thousand Oaks, CA, USA. In 2000, The National Institutes of Health became the principal sponsor of the Registry in the USA and the European Commission in Europe. We are very grateful to Amgen for the initiation of the Registry and support we have received over the years.

Since 2000, the SCNIR has continued its work on the causes, consequences and best treatments for severe chronic neutropenia with sponsorship from government sources, foundations and private gifts. The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), in the U.S. currently provides major support for the SCNIR. In Europe the SCNIR receives additional support from foundations and pharmaceutical companies for helping to generate safety reports on Filgrastim biosimilar products. The SCNIR depends on such grants and gifts to continue its work and will greatly appreciate your support if you find its efforts, programs and services useful for you, your family and your community.

In this handbook, “you” refers to you/your child.

Throughout the text there are words and phrases that appear in Italics, these are explained further in the glossary.

How the blood is formed

The bone marrow is where all blood cell production takes place.

The bone marrow, as its name indicates, is located within the bones. The skeleton of the adult human body is built of different types of bones. The bones of arms and legs are long bones with an inner cavity housing
mainly fatty tissues, nerves and blood vessels. The marrow in the long bones is of yellow color and because of its fat content is referred to as yellow or fat marrow. This yellow marrow is not actively involved in the production of blood cells in an adult.

The red, blood-forming marrow is located within a different type of bone that is flat like the breastbone and the pelvic bone. These bones are not hollow inside, but contain sponge-like scaffolding made from bone substance. The gaps in-between the bone structures are filled with little nests of blood-forming cells, supporting cells, and a network of nerves as well as small nourishing blood vessels. The medical term for the formation of blood cells is hematopoiesis (Figure 1).

There are three basic types of blood cells:

The red blood cells (erythrocytes) carry oxygen from the lungs to all tissues of the body.

The platelets (thrombocytes) are essential for the clotting of the blood.

The white blood cells (leukocytes) are in charge of the body’s defense against infections. There are three main types of white blood cells: granulocytes, monocytes and lymphocytes. Neutrophils normally make up the major part of the granulocytes.

The growth and development of the blood is controlled in the bone marrow in order to produce the correct number of each type of cell to keep the body healthy. About three million red and 120 thousand white blood cells are produced every second. The mature cells leave the bone marrow, enter the blood stream and circulate with the blood through the body. All different blood cells are derived from a single type of cell called the hematopoietic stem cell (which is distinct from the embryonic
stem cell that can produce all cells and tissues of the body). Only a very small proportion of bone marrow and blood cells are stem cells. These are the cells that need to be collected for hematopoietic stem cell transplantation (HSCT), often called bone marrow transplantation (BMT).

Figure 1. All types of blood cells are derived from one single ‘mother cell’, the pluripotent hematopoietic stem cell. ‘Pluripotent’ means the cell can produce many different blood cell types.

All blood cells eventually die, but their life spans vary amongst the different types of cells. Red blood cells live for approximately four months after they leave the bone marrow, whereas platelets live for just a few days and granulocytes (neutrophils) for only a few hours.

What is Neutropenia?

The term neutropenia describes the situation where the number of neutrophils is too low. Neutrophils play a crucial role in the body in
combating bacterial infections. A reduced number of neutrophils thereby increases the susceptibility to bacterial infections (Figure 2).

To calculate the absolute neutrophil count (ANC) the percentage of neutrophil granulocytes (% segmented neutrophils + % band neutrophils) needs to be multiplied with the total number of white blood cells (WBC) divided by 100, as seen in the formula below:

\[
ANC = \frac{\left(\text{segmented neutrophils} \% + \text{band neutrophils} \%\right) \times \text{total WBC count}}{100}
\]

The blood of healthy adults usually contains about 1,500 to 7,000 neutrophils per µl (=1,5-7,0 x 10⁹/l). In children under 6 years of age the number of neutrophils can be lower. Neutrophil counts also vary by ethnic groups. Lower neutrophil counts are a common finding in people of African descent and some ethnic groups from the Middle East. This condition is called benign ethnic neutropenia and has no associated clinical problems.

Figure 2. An artist’s view of neutrophils attacking bacteria in the bloodstream.
Neutropenia is divided into three degrees of severity based on the absolute count of neutrophil granulocytes (ANC):

<table>
<thead>
<tr>
<th>Severity of Neutropenia</th>
<th>Absolute neutrophil count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Level between 1,000-1,500/µl</td>
</tr>
<tr>
<td>Moderate</td>
<td>Level between 5,00-1,000/µl</td>
</tr>
<tr>
<td>Severe</td>
<td>Level below 500/µl</td>
</tr>
</tbody>
</table>

Neutropenia can be differentiated by duration of the disease:
- Acute (short-termed, for a few days)
- Chronic (duration of more than 3 months)

Transient or Temporary Neutropenia describes a condition in which the neutropenia has resolved. The term Severe Chronic Neutropenia summarizes all types of chronic neutropenias, independent of the underlying causes.

**Symptoms of Neutropenia**

The patient’s symptoms depend on the severity of neutropenia. The lower the neutrophil count, the higher is the risk of infection. The risk increases further, if the neutrophil count is reduced for more than three days. Common infections are middle ear inflammation/otitis media, tonsillitis, ulcers of the oral mucosa, mucositis as well as skin abscesses. Pneumonia and abscesses of the inner organs such as kidney abscesses are less frequent. These infections can be life-threatening, if the patient remains permanently neutropenic. Therefore, it is crucial for neutropenic patients to consult a physician immediately in case of any sign of...
infection or inflammation (e.g. fever over 38.5°), and if necessary start an antibiotic treatment.

**Causes of Neutropenia**

There are many different causes of severe chronic neutropenia. Neutropenia can occur due to:

1. Chemotherapeutic treatment for cancer
2. Viral infections (e.g. cytomegalovirus, Epstein-Barr virus)
3. Pharmaceuticals (diuretic, sulphonamides, metamizole, griseofulvin, chloramphenicol, antibiotics, chemicals like benzol or toxic plants)
4. Inheritance: some people are born with neutropenia for genetic reasons (congenital)
5. Immunologic causes: antibodies against neutrophils

In some cases the cause remains unknown; physicians refer to that subgroup as “idiopathic Neutropenia”.

**Incidence of severe chronic Neutropenia**

All types of chronic Neutropenia are rare diseases. Primary autoimmune Neutropenia is found predominantly during infancy. However, there is no reliable incidence rate known. Congenital Neutropenia in contrast is very rare with 1-4 cases in 1 Million of inhabitants.
Basic information on heredity

In cells of any human being there are two genes, each with different features (allele), on which genetic characteristics are passed on to the offspring. One genetic characteristic originates from the father and one from the mother. Genes can be passed on by dominant or recessive inheritance:

**Autosomal dominant inheritance**, is a gender-independent way of transmission. One affected gene of the parent is sufficient to pass a characteristic or disease on to a child. Usually, the parent who passes on the affected gene is also affected by the disease. In any pregnancy there is a 50% probability to inherit the affected gene and to develop the disease. As an example *ELANE-CN* can be named.

**Autosomal recessive inheritance**, is another gender-independent transmission. Usually both parents carry an affected gene, but are not affected by the disease. Characteristics or illnesses require transmission of one affected gene by both parents. The probability that a specific characteristic or illness emerges in an offspring is 25% in any pregnancy. As an example *HAX1-CN* can be named.

Gene transmission by **X-linked recessive inheritance** is a gender specific transmission. Mothers are carriers of affected genes, but only boys are clinically affected due to their gender *chromosomes* XY.

Medical conditions normally follow these patterns of inheritance, but in addition there may be exception to these rules.

**Genetics of congenital Neutropenia**
In 1999, Horwitz and Dale from Seattle found mutations on the neutrophil-elastase gene (*ELANE*) via gene sequencing in patients with cyclic Neutropenia. Mutations scattered over nearly all gene sequences on the *ELANE*-gene have been found in most of the patients suffering from cyclic Neutropenia and in about 50% of patients suffering from *congenital* Neutropenia. Examinations of families reveal that there are spontaneous mutations as well as inherited mutations (*autosomal* dominant inheritance). Nevertheless, *ELANE* mutations have not been found in families in which an *autosomal* recessive inheritance was assumed.

Only few years later, Klein and Welte from Hannover discovered homozygous mutations on the *HAX1*-gene (*autosomal* recessive inheritance) in patients coming from the Middle East. Interestingly, these mutations could be identified also in remaining patients of the Swedish pedigree described by Rolf Kostmann.

In 2014, Klein discovered homozygous mutations on the *JAGN1*-gene (*autosomal* recessive inheritance) in a Sephardic community from Algeria, a community with Jewish ancestry. Later, mutations have also been found in patients from the Middle East. These patients present with similar phenotype to *ELANE*- and *HAX1*-CN.

Table 1 presents an overview of *congenital* gene defects in neutropenia subgroups.

However, with the decryption of the up-to-date known genetic defects, the research concerning rare diseases is still far from being completed. There is still a group of patients (approx. 30%) in which a genetic defect is not known yet and it is necessary to search specifically for clinical characteristics and specifics to identify new genetic subtypes.

**Table 1**: Gene defects in neutropenia
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Gene</th>
<th>recessive</th>
<th>dominant</th>
<th>Neutropenia plus</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELANE-CN</td>
<td>ELANE</td>
<td>-</td>
<td>+</td>
<td>Pre-leukemic Syndrome</td>
</tr>
<tr>
<td>Kostmann Syndrome</td>
<td>HAX1</td>
<td>+</td>
<td>-</td>
<td>Pre-leukemic Syndrome, CNS convulsions</td>
</tr>
<tr>
<td>JAGN1-CN</td>
<td>JAGN1</td>
<td>+</td>
<td>-</td>
<td>Osteoporosis, Heart Malformations, Exocrine Pancreatic Insufficiency</td>
</tr>
<tr>
<td>G6PC3-CN</td>
<td>G6PC3</td>
<td>+</td>
<td>-</td>
<td>Short Stature, Cardiac- and Urogenital Malformations, Translucent Subcutaneous Veins</td>
</tr>
<tr>
<td>Congenital Neutropenia with GFI1 Mutation</td>
<td>GFI1</td>
<td>-</td>
<td>+</td>
<td>B-/T-Cell defect</td>
</tr>
<tr>
<td>WHIM Syndrome</td>
<td>CXCR4</td>
<td>-</td>
<td>+</td>
<td>Myelokathexis, IgG Reduction Warts</td>
</tr>
<tr>
<td>Shwachman Diamond Syndrome</td>
<td>SDBS</td>
<td>+</td>
<td>-</td>
<td>Exocrine Pancreatic Insufficiency, Short Stature, Skeletal Abnormalities, Anemia, Thrombocytopenia</td>
</tr>
<tr>
<td>Barth Syndrome</td>
<td>TAZ1</td>
<td>X-linked</td>
<td>-</td>
<td>Dilated Cardiomyopathy, Skeletal Myopathy, Short Stature, 3-Methylglutaconic Aciduria</td>
</tr>
<tr>
<td>Neutropenia with WAS Mutation</td>
<td>WAS</td>
<td>X-linked</td>
<td>-</td>
<td>Monocytopenia, Normal Platelet Count</td>
</tr>
<tr>
<td>Glycogen Type 1b</td>
<td>SLC37A4</td>
<td>+</td>
<td>-</td>
<td>Hepatosplenomegaly, Hypoglycemia, Lactic Acidosis</td>
</tr>
<tr>
<td>Hermansky-Pudlack Syndrome</td>
<td>AP3B1</td>
<td>+</td>
<td>-</td>
<td>Partial Albinism, Short Stature, IgG Reduction, Hemorrhagic Diathesis</td>
</tr>
<tr>
<td>Hermansky-Pudlack-like Syndrome</td>
<td>multiple</td>
<td>+</td>
<td>-</td>
<td>Partial Albinism, Short Stature, IgG Reduction</td>
</tr>
<tr>
<td>Griscelli Syndrome</td>
<td>RAB27A</td>
<td>+</td>
<td>-</td>
<td>Hemophagocytosis</td>
</tr>
<tr>
<td>Chediak-Higashi Syndrome</td>
<td>LYST</td>
<td>+</td>
<td>-</td>
<td>Albinism, T-/NK-Cell and Chemotaxis defective</td>
</tr>
<tr>
<td>Hyper IgM</td>
<td>CD40LG</td>
<td>X-linked</td>
<td>-</td>
<td>IgG, IgA, IgE Reduction</td>
</tr>
<tr>
<td>Congenital Neutropenia with VPS45 Mutation</td>
<td>VPS45</td>
<td>+</td>
<td>-</td>
<td>Nephromegaly, Splenomegaly, Osteosclerosis, and Neurological Abnormalities</td>
</tr>
<tr>
<td>Congenital Neutropenia (unclassified)</td>
<td>unknown</td>
<td>?</td>
<td>?</td>
<td>Increased IgG Levels</td>
</tr>
</tbody>
</table>

**Types of Severe Chronic Neutropenia**
Severe chronic neutropenia can either exist from birth (congenital neutropenia) or can develop at any time throughout life (acquired neutropenia). It can occur isolated as well as in association with other symptoms of a different underlying disease. The genetic subgroups are described in detail in the chapter “Genetics of congenital Neutropenia”. In the following list examples of different types of neutropenia are presented:

- Congenital Neutropenia
  1. Severe congenital neutropenia (e.g., ELANE-CN; HAX1-CN, JAGN1-CN) also known as “Kostmann syndrome”
  2. Cyclic neutropenia
  3. G6PC3 and other genetic subtypes

- Metabolic diseases associated with Neutropenia
  1. Shwachman-Diamond syndrome
  2. Glycogen storage disease
  3. Barth syndrome

- Immune disorders associated with Neutropenia:
  1. Myelokathexis/WHIM syndrome
  2. Wiskott-Aldrich syndrome

- Acquired neutropenia
  1. Idiopathic neutropenia
  2. Autoimmune neutropenia

**Severe Congenital Neutropenia**

*Congenital* Neutropenia, often referred to as *Kostmann syndrome*, is a rare type of neutropenia which is already present at birth. It is an inherited disease and therefore more than one family member can be
affected. Nevertheless, *sporadic* occurrence in only one patient of a family is also possible. Prenatal genetic diagnostics to detect a disease prior to birth may be available for families in which a specific gene mutation was identified. The question whether the detection of a neutropenia associated gene mutation should be an indication for an abortion is not answered yet and should be discussed with experts, ethics boards and family carefully.

**Figure 3.** In healthy individuals, the maturation of neutrophilic granulocytes leads to segmented neutrophils, which leave the bone marrow and enter the blood. In congenital neutropenia patients the maturation pathway is blocked at the stage of early precursor cells, the promyelocytes.

*Congenital* neutropenia is usually severe and neutrophil *granulocytes* are often completely absent in the blood of these patients at the time of diagnosis. Patients who are diagnosed with *congenital* neutropenia usually show what is known as a maturation arrest (*Figure 3*) in the early stage of neutrophil development (myelopoiesis), in the *bone marrow*. This means that their *neutrophils* rarely fully mature into the cells, that are capable of fighting infections.
Without treatment these patients suffer from severe bacterial infections such as infections of the umbilical stump (omphalitis), recurrent bronchitis, pneumonia, skin abscesses or middle ear inflammations (otitis media) – often already during the first months of life. Thus, in most patients congenital neutropenia is diagnosed during infancy. G-CSF treatment usually results in a long-term increase in peripheral blood neutrophil counts and protects from bacterial infections (see chapter G-CSF treatment).

**Cyclic Neutropenia**

Cyclic neutropenia is another inherited type of neutropenia. As the name indicates, in this disease neutrophil counts show a cyclic pattern with a typical length of 21 days. These cycles vary from patient to patient. With some individuals being neutropenic during the whole cycle whereas others have low neutrophil counts for only a few days and normal blood counts during the rest of the cycle (Figure 4). The frequency of bacterial infections depends on the length of the neutropenic period that the patient experiences. Those who have a longer neutropenic period within the cycle suffer more frequently from infections compared to patients who have only short neutropenic phases.
If infections, *fever* or aphthous stomatitis (inflammation and *ulceration* of the mouth) occur frequently in approximately three-week intervals, a diagnosis of cyclic neutropenia should be considered and serial *differential blood counts* need to be performed (at least 3 times per week over a period of 6 weeks) to search for the cyclical pattern of blood neutrophils in this disease.

Almost all patients with cyclic neutropenia have periods of severe neutropenia (ANC less than 200 cells per µl [0.200 x 10^9/L]) every three weeks with some symptoms almost every cycle, but significant infections (e.g., pneumonia or bacteraemia) usually are infrequent. Cyclic neutropenia occurs because of fluctuating rates of cell production by the *bone marrow stem cells*. In contrast to other causes for neutropenia, in this condition the *bone marrow* changes during the cycle, between normal appearance to that of severe maturation arrest of neutrophil production. Other *blood cells*, such as *platelets* or red cells, can also show oscillations with a cyclical pattern. Patients with cyclic neutropenia benefit from G-
CSF treatment (chapter “Treatment of Subtypes of Severe Chronic Neutropenia”), usually requiring lower doses than those used for severe congenital neutropenia. G-CSF therapy does not prevent from the cyclic course of neutrophils. It shortens the cycle length from usually 21 days to about 14 days. The goal of the G-CSF therapy in cyclic neutropenia is shortening the nadir (the time when the ANC is below 500/µl) to less than 3 days, that infections cannot develop. In 50% of patients with CyN, autosomal changes in the ELANE gene were identified. In ELANE negative patients the genetic cause remains still unknown. So far, different mutations in the ELANE gene have been detected. Some ELANE mutations are identical in cyclic and congenital neutropenia.

**Shwachman-Diamond Syndrome (SDS)**

SDS is a rare autosomal recessive inherited condition with multisystemic abnormalities including hematopoietic changes (mainly Neutropenia), pancreatic insufficiency (problems with digestion of fats in the diet resulting in large volume fatty stools), failure to thrive (short stature), psychomotor retardation or neurological features and a varying degree of congenital abnormalities including the skeleton, liver, heart and the immune system.

In 2003, mutations in the SBDS-gene have been found to be associated with this condition. The symptoms of SDS can vary from patient to patient at the time of diagnosis. In the majority of patients, SDS is diagnosed in infancy. SDS must be considered even if clinical symptoms of pancreatic insufficiency are absent, as a significant percentage of patients develop pancreatic insufficiency at a later stage or their symptoms may have resolved prior to diagnosis of neutropenia.

If neutropenia gets severe (long-term neutrophil counts under 500/µl), these patients also suffer from recurrent bacterial infections and treatment
with G-CSF is helpful. Most G-CSF treated patients respond with an increase in blood *neutrophils* and reduction of infectious episodes. In SDS, other blood cell numbers may also be decreased to a varying degree (potentially leading to *anemia* and/or *thrombocytopenia*).

As already mentioned for patients with congenital neutropenia, patients with SDS have also an increased risk in developing leukemia, therefore, it is strongly recommended to have bone marrow examination with cytogenetic testing on a yearly basis.

#### Metabolic Disorders with Neutropenia

**Glycogen storage disease type 1b** is a rare, autosomal recessive inherited metabolic disorder which affects the breakdown of glycogen, a storage form of glucose (sugar). The liver, spleen and other tissues accumulate glycogen. Patients present with enlarged liver and spleen, failure to thrive, kidney problems, hypoglycemia (low blood sugar) as well as recurrent infections. The presence of an enlarged spleen can be associated with low red blood cells causing *anemia* and *thrombocytopenia*, whereas neutropenia is always present. Chronic neutropenia in these patients is accompanied by a defective function of the cells that are responsible for the killing of *bacteria* (defective function of the *neutrophils*). As a result of G-CSF treatment, patients do not only respond with an increased ANC, but also with improved activity of their *neutrophils*.

**G6PC3-CN**

Chronic Neutropenia caused by mutations in the G6PC3-gene is also an autosomal recessive inherited disorder and is very rare. G6PC3 stands for Glucose-6-Phosphatase, Catalytic Subunit 3 – a gene, which regulates the
enzymatic activity of Glucose-6-Phosphate. However, this gene does not induce/trigger changes in sugar metabolism – as present in the Glycogen storage disease type 1b. Apart from neutropenia those patients also suffer from short stature or developmental delay, cardiac and urogenital malformations, translucent *subcutaneous* veins as well as inner ear hearing loss.

### Idiopathic Neutropenia

The term ‘idiopathic neutropenia’ describes various types of neutropenia which may occur at any point in life for unknown reasons. As already described for the other types of neutropenia, frequency and severity of infections is correlated with the neutrophil counts. Neutrophil counts and clinical problems in these patients vary considerably, but in general the more severe the neutropenia the more serious and frequent the infections. Most patients respond well to G-CSF treatment, but require a long-term treatment.

### Autoimmune Neutropenia

In neutropenic children aged 6 months to 4 years the presence of neutrophil-specific *antibodies* can result in increased destruction of the body’s own *neutrophils*. This process, termed *autoimmune* neutropenia (AIN) is the most common cause for neutropenia of this age group. The reason for the development of *antibodies* against the own body is still unknown. Infections may be involved in the development of AIN. Although these infants often have very low absolute neutrophil counts, they usually do not suffer from severe bacterial infections. Patients should be kept under medical care, but may not necessarily require treatment with antibiotics or G-CSF. In some cases, this subtype of
neutropenia is diagnosed by coincidence (e.g. drawing blood for routine purposes) – in this case the child does not suffer from severe infections.

Irrespective of ANC, but depending on the frequency of bacterial infections, a prophylaxis with an oral antibiotic (e.g. Cotrimoxazol) may be beneficial. The few children who develop severe infections or have significant impairment of life (e.g. frequent visits to emergency rooms), treatment with G-CSF is almost always effective. Nevertheless, most of the patients with primary AIN do not need any therapy.

Vaccinations, including live vaccines, should be given timely according to the recommended immunization schedule.

Children with AIN can participate in normal daily life activities, e.g. can attend day care, etc.

The prognosis of primary autoimmune neutropenia is markedly good as the antibodies spontaneously disappear in most cases during infancy or at the latest when the child reaches the early school age. In most children the blood counts normalize by age 3-5 years. So far, none of the described patients developed subsequent immune diseases.

Autoimmune neutropenia may also be seen in adults, predominantly in young women (secondary AIN). The adult type of autoimmune neutropenia is less likely to resolve spontaneously and more likely to be associated with other autoimmune disorders.

Autoimmune neutropenia is usually diagnosed by the detection of anti-granulocyte antibodies in the blood. The absence of a positive test to these antibodies does not rule out the diagnosis of autoimmune neutropenia, nor does a positive test completely rule out congenital neutropenia. Therefore, in case of repeated negative test results and/or additional abnormalities of other blood counts (e.g. low platelet count) or
unusual or severe bacterial infection, a bone marrow aspiration is warranted to rule out congenital neutropenia

**Neonatal Alloimmuneneutropenia (NIN)**

Alloimmuneneutropenia is a particular type of antibody-mediated neutropenia. During pregnancy little amounts of fetal blood may enter the blood circulation of the pregnant mother via the placenta. If those cells carry features which differ from the mother’s blood characteristics, antibodies can be produced by the mother’s immune system and passed on to the child’s blood stream via the placenta where they can induce destruction of the child’s neutrophils. After birth neutropenia can be noticed in the blood of the child; the mother’s blood count is normal. In the period of neutropenia bacterial infections can occur and hence antibiotic prophylaxis may be useful. Since those antibodies are just “borrowed”, they disappear on their own after approximately 11 weeks and the blood count normalizes. Theoretically, the formation of maternal antibodies can reappear in following pregnancies; thus the complete blood counts (CBC)/full blood count (FBC) of the sibling should be monitored.

**Other Conditions Associated with Neutropenia**

There is a number of other conditions which include neutropenia as part of the symptoms. Depending on the nature of the main condition the management of the neutropenia may differ from the treatment of ‘pure’ SCN.

The main conditions that may include neutropenia are:
- Severe *aplastic anemia*
- Fanconi anemia
- *Viral* illnesses
- Post *chemotherapy* or radiotherapy (radioactive exposure)
- Drug-induced situations (e.g. antibiotics, pain medications)

There are some other very rare disorders, *congenital* or acquired, that may be associated with neutropenia (e.g. *myelokathexis*, hyper IgM *syndrome* or severe combined immunodeficiency).

This list may be incomplete as there are constantly new insights on diseases associated with neutropenia.
Diagnostic Tests Used in Severe Chronic Neutropenia

When neutropenia is suspected (e.g. with recurrent infections which may occur on a cyclical basis), physicians will begin taking a *CBC/FBC* with differential and proceed further tests if necessary. These examinations will be extended to include the *bone marrow* of the patient. The most important investigations are explained below.

Blood Count Monitoring

As already mentioned, the first investigation on suspicion of neutropenia is a *CBC/FBC* in order to measure the absolute neutrophil count. If the neutrophil count is low it is common practice to repeat the *CBC/FBC* to be certain that the neutropenia continues. In patients with SCN the neutrophil count may vary slightly, but it always remains at a very low level in contrast to cyclic neutropenia. If the neutrophil count varies substantially, the physician may suspect cyclic neutropenia. To confirm the diagnosis the physician will arrange that blood samples will be taken 3 times per week for at least 6 weeks to see whether there is a regular cyclical pattern of neutrophil counts.

Other Blood Tests

The physician will also conduct a blood test to exclude *autoimmune* neutropenia by testing for *antibodies* (see chapter “Autoimmune Neutropenia”).

Detection of Antibodies
Testing the blood of a patient for *antibodies* should be conducted only by specialized laboratories as these tests are very vulnerable to interferences and negative results cannot certainly rule out *autoimmune* neutropenia.

**Molecular genetic analysis**

In case of a suspected *congenital*, inherited type of neutropenia, molecular genetic examination may be necessary to search for known gene mutation (see chapter “*Genetics of congenital Neutropenia*”). These examinations can be performed in a few specialized laboratories only. If there is evidence of a familial prevalence of neutropenia in your family, you should talk to your doctor about such analyses. The results should be discussed with the family and genetic counseling should be offered.

**Bone Marrow Aspiration/Biopsy**

If the patient’s blood tests indicate *congenital* neutropenia, it is important to perform a *bone marrow* examination to confirm the diagnosis by looking at the marrow cells under the microscope (Figure 5). Bone marrow cells are usually taken from the large pelvic bone, the ilium, or sometimes also from the flat breastbone, the sternum. In Infants, it can be collected from the shin bone, the tibia. This is usually carried out under general anesthetic or under local anesthetic with sedation. The performed technique may vary between treating centers. Your physician will explain exactly which procedure will be used for you.

There are two different methods to examine *bone marrow*. Firstly, marrow cells can be taken out like taking a blood sample from a vein, but this time from the middle of the bone (*bone marrow* aspirate). Secondly, a small piece of solid, bonier part of the *bone marrow* is taken (*bone
marrow biopsy) and processed differently, to look at the architecture of the marrow structure.

The material taken at a bone marrow aspiration is a sample used for smears in order to make the bone marrow cells visible under the microscope (morphology). In addition, bone marrow samples are used for further examinations such as cytogenetic analyses (not to be confused with genetic analyses) or investigations of the G-CSF (Granulocyte-Colony Stimulating Factor) receptor genes. If possible, an additional sample is sent to cell bank of the SCNIR, where it will be frozen to be available for future research projects (see chapter “Registry”).

![Figure 5](image)

**Figure 5.** Bone marrow smear of a patient with absence of mature neutrophils (right) compared to the bone marrow of a healthy patient with all maturation levels of neutrophils (left).

### Samples of the Bone Marrow (Morphology)

After staining the bone marrow smears, the different cells are counted and their shapes are assessed. Sometimes, malignant cells (*leukemia* cells) can be detected in smears even before they appear in blood examination.
Cytogenetic Evaluation and Molecular Testing

In a cytogenetic examination, the chromosomes of the bone marrow cells are analyzed. Changes detected in chromosomes of these cells may be harmless, but in some cases they indicate a transition to leukemia. As previously mentioned, it is important to monitor the cytogenetics of the marrow cells, as changes in the chromosome pattern may develop before any abnormalities of bone marrow cells appear. In order to recognize the development of leukemia at an early stage such examinations are crucial. Therefore, an annual bone marrow check-up is recommended. In the majority of patients suffering from neutropenia the results are totally normal. Fig. 6 shows two chromosome patterns, so called karyotypes, with a normal and with cytogenetic abnormalities.

Figure 6. Every human cell (except ova and sperm) contains 2 pairs of 22 chromosomes as well as 2 additional sex chromosomes (women: XX, men: XY) as shown in the picture on the left. The loss of a specific chromosome indicates pre-leukemic changes, as shown on the right, using the example of monosomy 7.

Analysis of the G-CSF Receptor Gene

An analysis of the G-CSF receptor gene provides information on the structure of this receptor. The function of a receptor is to bind
extracellular molecules followed by the release of a signal into the cell, which leads for instance to cell division or maturation. The G-CSF receptor exists on all granulocytes and fulfills the task of binding the cytokine G-CSF to the cells. Thereby the starting signal for maturation, cell division or strengthening of various cells is passed on to the nucleus, the command center of the cell. In some patients with congenital neutropenia this receptor undergoes changes which can precede a transition to leukemia. Those modifications do not affect the response to G-CSF and can be detectable (for) several years before leukemia (finally) develops. Thus, this analysis is a crucial indicator for patients experiencing G-CSF receptor changes. Nevertheless, besides a G-CSF receptor analysis, regularly (at least once a year) bone marrow examinations including cytogenetics are recommended.

Investigations in Patients with Other Conditions

To be certain about the diagnosis of conditions not limited to the blood system (e.g. Shwachman-Diamond syndrome, glycogen storage disease type 1b and others) investigations beyond blood and bone marrow tests may be necessary. Your physician will explain which further tests are required. In some cases this may involve referrals to other specialists.

Severe Chronic Neutropenia (SCN) is a rare disease. Some centers are in addition to treatment also actively involved in research of SCN and therefore may be able to provide further examinations and to discuss with patients.

Treatment of Subtypes of Severe Chronic Neutropenia

The main goal of any treatment for SCN patients is to enable a normal life in every way including school, leisure, family or professional life.
In first place a correct diagnosis is fundamental for a decision on the treatment of SCN.

Treatments which are used in the management of congenital, cyclic and idiopathic neutropenia include:

- Granulocyte-colony stimulating factor (G-CSF)
- **Hematopoietic stem cell transplantation** (HSCT; also called *bone marrow* transplantation)
- Others, including:
  - other cytokines
  - antibiotics
  - corticosteroids*
  - immunosuppressive drugs*
  - immunoglobulins
  - vitamins
  - white cell transfusions

* Treatment with these agents is generally not recommended, except for patients with rheumatological conditions (e.g. lupus), as they impair other parts of the immune system.

- Supportive care, discussed below

Treatments prescribed by your physician are extremely important to decrease the potential for infection. Apart from the therapy prescribed by your physician, good nutrition and hygiene (including good dental hygiene) are extremely important to decrease the risk of infection. However, nutritional treatments (a healthy and balanced diet) alone will not raise the neutrophil count in severe chronic neutropenia.

Patients should discuss specific treatment options with their physicians. These discussions should include the benefits of treatment as well as potential risks and side effects.
The majority of SCN patients benefit from treatment with granulocyte-colony stimulating factors (G-CSF). To prevent bacterial infections hematopoietic growth factors (cytokines) can be started directly after diagnosis. An acute/existing inflammation, though, still needs antibiotic therapy in addition to G-CSF therapy.

**Granulocyte-Colony Stimulating Factor (G-CSF)**

G-CSF is a cytokine normally produced by the human body itself. G-CSF, which is given as treatment, is NOT from human beings, but is safely manufactured (by genetic engineering) to produce an identical substance that has all the normal activity and function of the naturally-occurring cytokine. Therefore, there is no risk of viral infection from G-CSF therapy.

G-CSF stimulates the production and at the same time enhances the activity of mature neutrophils i.e. improving their bacteria-killing function. It operates via a receptor localized on granulocytes which binds the G-CSF to the cell and signalizes the cell to mature, to divide or to enhance function.

SCN patients produce their own G-CSF, but much higher doses of G-CSF are required to compensate the lack of neutrophils. It is still unknown why this endogenous G-CSF is not sufficient. Thus, additional (as a drug added) G-CSF is required.

The dose and frequency of G-CSF injections required to increase and maintain the neutrophil count to 1,000 per µl (1 x 10⁹/l) varies widely. For most patients, G-CSF given at 5-20 mcg/kg/day (micrograms per kilogram of body weight per day) as a daily subcutaneous injection (i.e. an injection just under the skin) is sufficient. Some patients need very
high doses, even up to 120 mcg/kg/day – potentially applied in more than one injection per day or even by continuous i.v. infusion – and some will require very low doses, as low as 0.01 mcg/kg/day. For some patients with severe chronic neutropenia the frequency of administration of G-CSF may be required less than daily, but short-term amendments may be necessary if illness due to infection occurs.

The required dose should be determined by a specialist and should be adapted according to the monitored ANCs.

G-CSF is usually administered by subcutaneous injection. Among for an injection recommended body parts are the abdomen below the naval, upper outer arms and upper outer thighs (Figure 7). It is possible to self-administer G-CSF which should be encouraged as it promotes a sense of independency and control over at least one aspect of treatment. As with any frequent and regular subcutaneous injection, rotation of the sites is recommended to prevent scarring and discomfort to the patient. The injection is usually not painful, but nevertheless occasionally a stinging sensation may be experienced for a short period of time on administration.

Administration of G-CSF may result in a dramatic increase in the numbers of neutrophils in the blood and is without doubt the most effective therapy in treating SCN. Some SCN patients receiving G-CSF (predominantly adults) report bone or muscle pain and splenomegaly. Other side effects are infrequent, but a few patients have experienced thrombocytopenia, injection site reactions, vasculitis, blood and/or protein in the urine and rarely an exacerbation of pre-existing skin disorders (e.g. psoriasis).
If one of these or other side effects occur, the patient’s doctor should be notified. With the lowest dose needed and daily injections bone and muscle pain usually disappear.

In addition, cytogenetic abnormalities, transformation to myelodysplastic syndrome (MDS) and leukemia have been observed in patients with congenital neutropenia treated with G-CSF. Current results of research indicate an association between the leukemia risk and the underlying genetic defect (see chapter “Prognosis”).

**Hematopoietic Stem Cell Transplantation**

HSCT is the only curative treatment option for SCN. It may be considered for failure to respond to treatment or for patients who develop MDS or leukemia in the course of their disease. Transplantation is a very intensive procedure, carrying serious risks and is therefore not recommended as treatment of first choice. It is important for the patient and physician to discuss in detail risks and benefits of this procedure. Regarding this issue the doctor in charge is able to give further information.
The HSCT procedure includes chemotherapy to eliminate the abnormal bone marrow, and then infusion of the donor’s bone marrow through an intravenous (iv) catheter, much like a blood transfusion; no surgery is involved. Often, long-term medical management is necessary after transplant to treat or prevent complications of the procedure. The donor, who may be a close relative or a matched volunteer, provides the necessary hematopoietic stem cells from bone marrow (multiple needle punctures, under anesthesia) or blood (run from one vein, through a cell separator, and returned to another vein by a process called pheresis). Hematopoietic stem cells can also be obtained from frozen, stored umbilical cord blood units, which also need to be matched to the patient’s tissue type. Hematopoietic stem cells are distinct cells, capable of reconstituting the blood and immune systems, but different from embryonic stem cells that could theoretically form an entire organism.

Other Treatments

Corticosteroids:
In some conditions steroids have long been effective in increasing neutrophil counts in the blood. Steroids work by stimulating neutrophils to leave the bone marrow and enter the blood stream. However, they do not induce the production of new neutrophils in the bone marrow. They may even decrease the function of neutrophils and the number of other types of white cells, thus, increasing the risk of infection and mask an existing leukemia. In general, the effectiveness of steroids for patients with SCN has not been proven useful.

White cell transfusions:
White blood cell transfusions are rarely used. They are generally reserved for severe life-threatening infections. For various reasons the replacement of neutrophils by transfusion is not feasible in the long-term. The collection of these cells is quite difficult and can only be performed in
specialized clinics. Furthermore, mature *neutrophils* have quite a short life span and cells cannot be stored for more than a few hours.

In patients experiencing a life-threatening infection, *granulocytes* donated by previously G-CSF treated patients can be transfused. The survival time of *neutrophils* is extended by treating the donor with G-CSF. Moreover, as with all transfers of blood products, a possible risk for transmission of *viral* infections such as hepatitis exists.

**Supportive Treatment**

There are a variety of supportive therapies; only the most important are listed below:

- *Mouth care*: this should include regular dental check-ups. Excellent oral hygiene is very important and the use of an antibacterial mouthwash is recommended.

- *Immunizations and vaccinations*: people with SCN have an intact immune system which produces normal *antibodies* protecting against devastating effects of *viral* illnesses. Therefore, all routine immunizations according to the standard vaccination schedule of your country are recommended.

- *Monitoring temperature*: in the case of a *fever* above 38.5°C/101.3°F the patient must seek medical attention.

- *Good general hygiene*: including thorough hand washing.

- *Prompt contact with physicians/hospitals/clinics*: it is important to have telephone numbers of the hospital, the doctor in charge and the SCNIR easily accessible at any time.
• Foreign travel: concerns such as special precautions, emergencies and contact telephone numbers should be discussed with your physician. You can find a list of neutropenia experts cooperating with the SCNIR in different European countries on our website [www.severe-chronic-neutropenia.org](http://www.severe-chronic-neutropenia.org).

Nevertheless, normalization of the neutrophils in severe chronic neutropenia cannot be achieved just simply through supportive measures.
Prognosis

Nowadays, new patients suffering from severe congenital neutropenia are treated with G-CSF immediately after diagnosis. This treatment leads to an increase of the neutrophils well above (the target level of) 1,000/µl in more than 90% of the patients, which protects sufficiently from severe bacterial infections. To date, the life expectancy is prolonged and patients have adulthood; a final assessment regarding the life expectancy is currently not available as G-CSF therapy is applicable only since the late 1980s.

Secondary Leukemia

Even before G-CSF therapy was available, sporadic reports have been published on leukemia in patients with congenital neutropenia. Due to the short life expectancy of most patients back then, the actual risk of leukemia could not be determined.

According to the current state of knowledge, in some genetic subtypes of neutropenia more than 10% of patients develop leukemia in the course of their disease. Leukemic progression is not restricted to patients with ELANE-associated severe congenital neutropenia. It still remains unknown whether today’s increased life expectancy only reveals the risk of leukemia in these neutropenia types or G-CSF has an additional influence on the development (e.g. favor the growing of a malignant cell clone). Based on current findings, a direct association between the risk of leukemia and the disease severity exists. Furthermore, there seems to be an association between leukemia and the causative gene mutation. Therefore, Severe congenital neutropenia can be categorized as a pre-leukemic condition. Patients may develop predominantly acute myeloblastic leukemia, but acute lymphoblastic leukemia and chronic myelomonocytic leukemia have also been reported.
In the 2017 data analysis of the European branch of the SCNIR, 17 out of 118 patients with ELANE mutations (14.4%) and 6 out of 48 patients harbouring HAX1 mutations (12.5%) have developed leukemia. Of the 88 patients with Shwachman–Diamond syndrome, 7 patients developed leukemia (9%). However, the number of patients in most other genetic subgroups of congenital neutropenias is still too small to make a final conclusion about the risk of developing leukemia.

The exact diagnosis as well as knowledge of risk factors and long-term prognosis is of great importance for an adequate therapy, long-term care and prognosis of the patient. Detailed consultations are offered by the SCNIR headquarter in Hannover, Germany. Screening for early risk factors, like G-CSF-receptor, RUNX1 and other mutations is advised.

**Note:** The aforementioned risk rates are statistical quantities. They only represent an important and applicable statement for the totality of patients suffering from neutropenia/the total population (group) of neutropenia patients. Leukemia can also progress quite unexpectedly under favourable or unfavourable conditions.

**Long-term Management and Monitoring of Severe Chronic Neutropenia**

As mentioned in the chapter “treatment of subtypes of neutropenia”, the key issue in treatment of SCN is “normalization of life” and the promotion of a ‘normal life’ for you. This includes schooling, vacations, family as well as social life. Administering G-CSF allows neutropenic patients to continue daily life tasks without the risk of dangerously low levels of neutrophils.
CBC/FBC evaluations provide the physician the information needed to monitor your ANC. Based on the monitored ANC the physician can adjust the G-CSF dose if required.

ANC Monitoring

When G-CSF treatment is initiated, your doctor will monitor your ANC closely, generally for the first 4 to 10 weeks to assure that the dose of G-CSF is appropriate for you. The registry suggests that when the dose has been stabilized, the SCN patient should be monitored with a CBC/FBC every 3 months. For patients on a daily administration of G-CSF, blood should be drawn approximately 18 hours after applying. Patients receiving G-CSF in intervals of more than 24 hours should have CBC/FBC done right before the next administration. This allows the physician to monitor the ANC at its lowest point.

Bone Marrow Monitoring

The international SCN registry advises to conduct at least once a year a check-up examination of the bone marrow cells including a cytogenetic examination in any patient with congenital neutropenia or patients receiving long-term treatment with G-CSF. For patients not receiving G-CSF treatment, the need of an annual bone marrow examination should be considered from patient to patient by the doctor in charge, dependent on the genetic subtype.

Periodontitis

Inflammations, aphthae (canker sores) or swelling of the oral mucosa as well as early degeneration of the jawbone with loose teeth up to premature tooth loss were frequently reported in SCN patients before
starting treatment with hematopoietic growth factors. These symptoms can be explained by the lack of defence against bacterial infections. Nevertheless, even under permanent G-CSF therapy, some patients continue to develop periodontitis which is usually due to an insufficient G-CSF dose or irregular use of this medication.

Pregnancy

The SCNIR collects information on pregnancies of SCN patients or partners of male SCN patients. The number of pregnancies reported to-date is relatively small. However, retrospective analysis of reported pregnancies showed that G-CSF treatment during pregnancy is safe for the unborn child.

There is no evidence for increased miscarriage or malformation in neonates due to G-CSF treatment. Therefore, it is recommended by experts of the international SCN registry to administer G-CSF over the course of pregnancy, in order to prevent infections. As G-CSF crosses the placental barrier, G-CSF treatment during the late phase of pregnancy may also prevent newborns with inherited neutropenia from perinatal infections. Since new information regarding pregnancies of registered patients are continuously added to the registry’s databank, patients are advised to consult their doctor in charge and the SCN registry in case of pregnancy.

Psychosocial Issues

Outcome on daily life

Family dynamics, school and employment can be affected by the increased stress caused by the chronic illness of a family member. Families and patients with SCN may experience similar stress to those
found in families with a family member with diabetes, epilepsy, cystic fibrosis or other chronic conditions. In general, children with SCN will experience the normal milestones of childhood along with the added stress caused by having a chronic condition. Exceptions may occur in patients suffering from additional symptoms or organ involvements (e.g. Shwachman Diamond syndrome, glycogen storage disease type 1b etc.).

Patient Support Groups

SCN is difficult to diagnose. Some patients will have life threatening infections, others constant infections, while some experience only intermittent infections. There may be disruptions to normal family life because the untreated SCN patient may have unpredictable illnesses. Vacations or travel may be avoided or delayed because of the unpredictable nature of infections that may occur. Families may feel isolated from friends and community, needing to speak with other families that are dealing with this rare problem.

After the diagnosis of SCN the patient and family may experience the common feelings of confusion, bewilderment and possibly anger. Joining support groups, family- or professionally-led, will help with these feelings. Listed below are support groups dedicated to helping families and patients whose lives have been impacted by neutropenia.

Severe chronic Neutropenia – like any other chronic disease – can have a significant influence/impact on family, school and also on professional life. In particular cases (even) life-threatening infections, which require hospital treatment, can occur. Depending on the individual situation of the patient, the daily life can be impaired to varying degrees. Thus, patients and families respond to the diagnosis of “severe chronic neutropenia” in many different ways: The reactions can range from concern about the patient up to the fear of the entire family’s future. Sometimes rage and anger can persist in the beginning (why me/us?). At
this point it is important to clarify that a good attitude towards therapy and dealing responsibly with the disease is helpful for living a “normal life”. As an example, trips abroad (such as holyday trips) are still possible after consultation with the physician in charge and on basis of responsible planning. So there is no need for patients to isolate themselves from the outside world or even to resign. On the contrary it can be very helpful for most patients to contact other persons affected and to attend self-help groups (see links) to exchange concerns.

The priority for children of preschool age is to control their environment. At this age, children suffering of severe chronic neutropenia should already learn how to prevent infections best. This implies without a doubt good personal hygiene such as frequent hand washing. In addition, children as early as this age should be taught to clean small abrasions or scratches immediately and to seek treatment of adults. Of course supervisors such as childminders and/or nursery school teachers need to be informed about the child’s disease.

All school-aged children utilize school for socialization and academic development. This development is essential to help the child move through the milestones of childhood. A SCN child will need all caregivers (such as school teachers, school nurses, day-care providers, coaches etc.) to understand SCN. The SCNIR website (severe-chronic-neutropenia.org) provides information explaining SCN that you can share with caregivers.

For schoolchildren it is particularly important to be aware of their illness on the one hand, but on the other hand not to see their illness as a stigma. Dealing with the disease as normal as possible is best. Furthermore, it is of great importance to inform the teachers of the patient as well as the school management as comprehensively as possible. Hence, SCN patients can be prevented of potential prejudice and exclusions.
Puberty is probably the most difficult time in life of an adolescent. In this time, especially, when being “different” is of particular importance, some patients fear the disease could possible isolate them from their friends. In an attempt to prevent this, patients sometimes get the idea of simply ignoring their disease. They neglect due to the disease threatening dangers and possibly abort therapy. At this age the support of their parents with the aim to keep a positive attitude is especially important. Only someone who is confident can accept his “otherness”. In addition, parents should pay special attention during this time to spot possible changes in their children dealing with themselves as well as with others or in dealing with their disease as early as possible and to counteract in time. In such a case you should seek the advice of the physician in charge and maybe also the teachers.
Severe Chronic Neutropenia International Registry

Due to the low prevalence of each subtype of neutropenia the current knowledge regarding the characteristics and clinical courses was mainly achieved by the establishment of an international registry: The Severe Chronic Neutropenia International Registry (SCNIR) was established in 1994 and ever since it collects longitudinal data about the clinical course, secondary disease, treatment response and side effects of G-CSF therapy and complications like leukemia and stem cell transplantation in patients with congenital and acquired severe chronic neutropenia (SCN).

The European Branch of the SCNIR is based at the Hannover Medical School (Germany); an additional office for collecting data on SCN patients from the USA, Canada and Australia is located in Seattle (University of Washington, USA).

The main objective of the Registry is an as comprehensive as possible data documentation regarding the clinical course of all neutropenia subtypes in the whole world. The data is analyzed with regard to therapy and long-term prognoses.

The (scientific) management of the SCNIR is shared between Prof. Dr. Karl Welte (Hannover and Tübingen) and Prof. Dr. David Dale (Seattle). The data of the SCNIR is analyzed on a regular basis and discussed annually at the Advisory Board, which is panel of 15 international scientific experts and representatives of patient organizations. Based on the latest findings recommendations concerning diagnosis and care for SCN patients are formulated by the Advisory Board.
The European Branch of the SCNIR

Until 2017, the SCNIR built a network with so far, 23 European partner countries as well as Israel, Turkey and Morocco. Up to now, about 740 patients are enrolled in the SCNIR Europe (Table 2). This European network is coordinated by Dr. Cornelia Zeidler at the Hannover Medical School. Each partner country has at least one acknowledged expert in the field of severe chronic neutropenia, who cooperates with the SCNIR and is part of the European SCNIR consortium. A list of these so called Local Liaison Physicians located throughout European Countries can be found on our homepage (severe-chronic-neutropenia.org).

The European Branch of the SCNIR can be contacted via:

Severe Chronic Neutropenia International Registry
Medizinische Hochschule Hannover
Kinderklinik
D-30625 Hannover, Germany
Phone +49 (511) 557105
FAX +49 (511) 557106
E-mail info@scnir.de
Further information, registration forms, references/further readings (also for physicians) etc. can be obtained from:
www.severe-chronic-neutropenia.org
Table 2: Enrollment in SCNIR by countries

<table>
<thead>
<tr>
<th>Country</th>
<th>2017 (n=777)</th>
<th>2014 (n=647)</th>
<th>2011 (n=544)</th>
<th>2005 (n=403)</th>
<th>2000 (n=212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>26</td>
<td>21</td>
<td>18</td>
<td>13</td>
<td>*</td>
</tr>
<tr>
<td>Belarus</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Belgium</td>
<td>28</td>
<td>28</td>
<td>28</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>Croatia</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>*</td>
</tr>
<tr>
<td>Germany</td>
<td>324</td>
<td>275</td>
<td>215</td>
<td>138</td>
<td>69</td>
</tr>
<tr>
<td>Greece</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>10</td>
<td>*</td>
</tr>
<tr>
<td>Ireland</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Israel</td>
<td>17</td>
<td>17</td>
<td>16</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Italy</td>
<td>50</td>
<td>46</td>
<td>44</td>
<td>36</td>
<td>18</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Morocco</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>15</td>
<td>14</td>
<td>14</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Norway</td>
<td>19</td>
<td>19</td>
<td>19</td>
<td>14</td>
<td>*</td>
</tr>
<tr>
<td>Poland</td>
<td>19</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>*</td>
</tr>
<tr>
<td>Portugal</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Russia</td>
<td>24</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>*</td>
</tr>
<tr>
<td>Serbia</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>*</td>
</tr>
<tr>
<td>Spain</td>
<td>21</td>
<td>21</td>
<td>20</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Sweden</td>
<td>36</td>
<td>30</td>
<td>29</td>
<td>27</td>
<td>14</td>
</tr>
<tr>
<td>Switzerland</td>
<td>27</td>
<td>12</td>
<td>10</td>
<td>6</td>
<td>*</td>
</tr>
<tr>
<td>Turkey</td>
<td>43</td>
<td>37</td>
<td>19</td>
<td>5</td>
<td>*</td>
</tr>
<tr>
<td>UK</td>
<td>83</td>
<td>76</td>
<td>66</td>
<td>62</td>
<td>48</td>
</tr>
</tbody>
</table>
Support Groups

Support groups can help patients and their families to get in touch with other affected parties and thereby provide assistance with issues of dealing with their disease. Those groups can be reached either via the SCNIR or directly:

For the German speaking parts of Europe:
Interessengemeinschaft Neutropenie e.V.
Phone: +49-5175-1233
www.neutropenie-ev.de

Selbsthilfegruppe Glykogenose Deutschland e.V.
Phone: +49-2365-931406
www.glykogenose.de

Shwachman e.V.
Phone: +49-5132-589581
E-mail: jane.weyer@web.de
www.shwachman.de

In Italy:
The Association for Shwachman Syndrome
E-mail: aiss@shwachman.it
www.shwachman.it

In the Netherlands:
The Association for Shwachman Syndrome
E-mail: info@shwachman.nl
www.shwachman.nl
In the UK:
   Shwachman Diamond UK
   E-mail: family_matters@shwachman-diamond-uk.org

In Canada:
   Neutropenia Support Assoc. Inc.
   P.O. Box 243, 971 Corydon Ave.
   Winnipeg, MB, Canada R3M 3S7
   Toll Free (Canada & U.S.): +1-800-6-Neutro
   www.neutropenia.ca

In the USA:
   Severe Chronic Neutropenia International Registry
   University District Building
   1107 NE 45th Street, Suite 345
   Seattle, WA 98105
   Phone: +1-206-543-9749
   Tollfree: +1-800-726-4463 (inside the U.S. only)
   Fax: +1-206-543-3668
   www.depts.washington.edu/registry

   Shwachman-Diamond Syndrome Registry
   www.sdsregistry.org

   National Neutropenia Network
   www.neutropenianet.org

   Barth Foundation
   Toll Free: +1-855-662-2784
   www.barthsyndrome.org
Frequently Asked Questions and Answers
on Severe Chronic Neutropenia

Basic Questions

1) *Why does my child or I have SCN?*

Nobody truly knows how and why SCN develops. It is often, but not always, genetically inherited. To list all potential paths of inheritance is beyond possibilities of this booklet – especially as research has shown in recent years that more diverse ways of inheritance exist than first assumed.

In some families, for example, neutropenia occurs for the first time without any affected parent or other relatives. Therefore, it is recommended to consult with your doctor or contact the neutropenia registry in Hanover directly, if inherited neutropenia in your family is suspected.

2) *My child is suffering from congenital neutropenia: Is it mine/our fault because I/we passed on the gene?*

No, that is not true. However, it seems reasonable, if affected people deal with such questions due to emotional stress caused by a chronic disease – but they should not torture themselves. Hence, to be fully informed is of great importance and once more we recommend contacting your doctor and the neutropenia registry in Hannover. In addition, in some cases it can be useful to talk to a psychotherapist about this issue.
3) **Will my child with chronic neutropenia develop normally in regard to their growth and development?**

This question depends again on the individual cases – even if many children suffering from neutropenia develop normally, there can be also exceptions. As an example, children with metabolic diseases can be named, as in general, those children have various comorbidities. Thus, talk to your doctor in charge about this concern, as he might be able to give advice.

4) **What is the life expectancy of a child with chronic neutropenia? And how should I deal with the uncertainty associated with this question?**

Before the availability of G-CSF, patients with chronic neutropenia had many problems with (in some extent life-threatening) infection. Some individuals died from infection at an early age. Nowadays, patients are generally treated with G-CSF and therefore have a near-normal ANC which protects them from serious infections. Thus, the life expectancy is probably normal, although no general verdict is possible.

However, this response is maybe not sufficient, as the second question suggest: Even a small uncertainty can be very distressing under some circumstances. If you are bothered by this issue in such an extent that you feel restricted in your life and have the desire to talk about it, professional support of a private psychotherapist may be recommendable. Chronic illnesses can lead to significant restrictions and burdens in daily life – you know that best: One (Patients and their families) should not be afraid to seek support in order to cope with this.
Questions concerning the daily life

5) Despite the illness of our child, how can we live as normal as possible and thereby show our child how to cope with its illness?

Regarding this question, different levels can have to be considered: On the everyday level, it can be helpful to conduct the treatments for the disease (e.g. application of G-CSF) within rituals. Parents, as role models, dealing with the therapy (e.g. handling the application) as normal as possible can be helpful. By considering the treatment as normal as possible, the child’s feelings should not be overlooked. If necessary the feelings should be discussed with the child.

Furthermore, it is important to find the right amount of care towards the child: Using the necessary precautions on the one hand, but on the other hand not caring for the child too much and not, for example, prefer the child to the siblings. In the upcoming questions you find further recommendations regarding the right amount of care without giving the child a “special status” in particular situations. Such a “special status” would affect the child’s self-image – which should not be affected by the disease – in the long-term. On the contrary, a responsible awareness, to have a chronic disease should be part of many other aspects in life and self-image. Ideally, dealing with SCN responsibly and thereby learning skills other children acquire later their life can be seen as an important strength.

Finally, it can matter to ask what you, as a parent, think of the disease and what kind of feelings (as well as issues) associated with the disease emerge: anger, fear and uncertainty as well as the prior mentioned feelings of guilt. Maybe you are sometimes a little bit
jealous of families who are not affected. This is totally normal – even if it is often very hard: It may help to become aware of those feelings, learn how to handle them and above all to talk about the situation with other people. Otherwise a chance exists that children feel those hidden feelings as well as thoughts and partially adopt them.

6) My daughter, who is aged 7, wants to attend a camp. As she has severe congenital neutropenia and is receiving daily G-CSF that I use to administer to her, I am reluctant for her to attend. However, I also do not want her to miss out on these opportunities. Do you have any advice?

Basically, your daughter should be encouraged to participate in such events. Prior to the camp you should inquire with the organizer of the holiday camp, whether the G-CSF can be administered on site, for example by a local ambulant nursing service or a local physician. If the supply of medication/of the drug is ensured and the organizer has been informed about your daughter’s disease, participation should be possible/nothing stands in the way of participation.

7) Can my child participate in school activities and what should I tell the teachers?

Your treating doctor may suggest school activities (or athletic activities) your child should not participate in under special circumstances. If there are no restrictions in this regard, it is desirable for your child to participate in all (athletic and other) school activities. It is important that the school is aware of your child’s special situation and the diagnosis is carefully explained to the teachers.
Medical Questions

8) There are so many different names for the medication I administer to my child. Are those different drugs? I would be pleased, if you could clarify that.

Your observation is totally correct: There are several terms which in the end describe the same drug or rather the same substance.

This is a growth hormone for certain blood cells (granulocytes) which are not sufficiently present in the blood of people with neutropenia. Accordingly, this substance is called “granulocyte-colony stimulating factor” (G-CSF).

The first word/term describes blood cells whose growth should be stimulated. The term “colony” refers to the fact that these drugs are produced in cell cultures.

The substance G-CSF in turn is processed in diverse drugs by different companies. There are “Lenograstim”, “Filgrastim” and “Pegfilgrastim”. These drugs also have their trade names under which the drug is sold, so additional names occur.

It is very important to pay attention to the dosage forms of drugs as the concentration may vary depending on the manufacturer and the daily dose should be maintained unchanged, in case the drug brand is changed.

9) I am 27 years old and have cyclic neutropenia. For this, I receive G-CSF three times a week. My boyfriend and I are getting married in a few months and soon after we would like to start trying for a family. Can you give me any advice on the chances of our child having cyclic neutropenia?
The chance of your child also having cyclic neutropenia is 50% as long as your partner does not have cyclic neutropenia. This is due to the fact that cyclic neutropenia is inherited in an *autosomal* dominant pathway.

Clarifying further questions regarding pregnancies in SCN patients would go beyond the scope of this handbook. To guarantee the best possible treatment during pregnancy you should contact your doctor as well as your gynecologist in order to define the right therapy in consultation with the neutropenia registry in Hannover (see section “Pregnancy”).

10) *My son has been receiving G-CSF since he was diagnosed with severe congenital neutropenia three months ago. Although he feels much better he still tends to get breakthrough (intermittent) gingivitis and mouth ulcers, which cause him a lot of discomfort. Is there anything we can do to help alleviate his suffering?*

   Especially children may benefit from good mouth care including flossing and regular dental check-ups.

   In university hospitals there are also dentists who are specialized in the co-treatment of corresponding diseases such as neutropenia. The addresses of these dentists can be obtained from the SCN registry in Hannover. Furthermore, you can also receive information on self-help measures in the evening of infection there. In some patients rising the number of *neutrophils* by increasing the G-CSF dose could be useful. This issue should be discussed with the treating physician.
11) *My child is due for some vaccinations, is it safe for her/him to have them?*

In general, it is safe for your child to have vaccinations (including yearly influenza immunization). The recommended vaccinations should be conducted in children with severe chronic neutropenia. In terms of special questions (e.g. special additional vaccination) you should contact your doctor or the International SCN Registry.

12) *My child recently had an extremely bad case of flu which my doctor did not treat with antibiotics; however, when my son cut himself after falling the doctor did treat him with antibiotics. My doctor told me that flu was a different type of infection in which antibiotics would not be successful. I am now very confused as to what type of infections I must pay particular attention. Can you explain that please?*

Infections can be caused by different agents. Two major types of germs are *viruses* and *bacteria*. A flu, for example, is caused by *viruses*. If, on the other hand, skin incisions get inflamed, this happened mostly through *bacteria*. Your child has a reduced number of *neutrophils* and hence is at greater risk of developing bacterial infections (usually the neutrophil *granulocytes* fight against them). Bacterial infections are treatable by antibiotic therapy. In contrast, *viruses* cause most colds, flu and other childhood illnesses such as chickenpox. Antibiotics cannot treat these diseases. *Viruses* are eliminated by *lymphocytes* which usually are not reduced in your child’s blood. So neutropenia patients usually have normal immune responses to *viral* infections.

If you have any doubt about the type of infection your child has, you should take him to his physician.
13) *When should my child commence G-CSF?*

Your child should start G-CSF therapy if he/she is suffering from frequent mouth ulcers or infections and has thereby a restricted quality of life – regardless of how much the ANC is reduced. Children suffering from *congenital* neutropenia with an ANC constantly under 500/µl over a longer period (more than 3 months) should definitely receive G-CSF as those patients have a high risk of infection. People differ: the same neutrophil count in different individuals may result in different numbers of infections. The major objective is to reduce the number and seriousness of infections in your child no matter how high his/her neutrophil count before treatment is.

14) *How long can you be safely treated with G-CSF?*

The SCNIR has information on many individuals who have received long-term G-CSF treatment. Furthermore, most of the patients have to use G-CSF until the rest of their lives to maintain a sufficient neutrophil count. Data regarding the medication risk collected and analyzed since the late 1980s indicates that long-term G-CSF therapy is safe and remains effective.

15) *Is it safe to have surgery whilst on G-CSF?*

Yes, it is okay to have surgery as long as the surgeon is fully aware of your condition and G-CSF treatment. You should obtain medical clearance from your hematologist prior to elective surgery and receive advice regarding your G-CSF dosing and schedule (if necessary adapt your G-CSF dose according to his advice of the upcoming operation).
16) *Will a certain diet improve my disease?*

A good balanced diet will be beneficial for your family’s overall health as it will provide essential nutrients and vitamins to ensure good health and as well promote normal growth and development. There are no known vitamins, herb supplements or special diets that approved to help increasing the neutrophil level.

17) *Where and how can I get in contact with other patients? Where do I find further information?*

Contact information (including websites and phone numbers) for patient support groups in Germany or other countries can be found on our homepage ([www.severe-chronic-neutropenia.org](http://www.severe-chronic-neutropenia.org)) as well as in this patient manual.

18) *Where can I find more literature on the disease?*

The SCNIR web page has a reference list with (mainly) English literature; in addition you can obtain literature by contacting the offices of the registry.
Glossary

**Abscess**, inflammatory process of the skin and mucous membranes with accumulation of pus.

**ANC (absolute neutrophil count)**, determined by adding the percentage of segmented neutrophils in the blood to the percentage of *bands* in the blood, multiplying that number by the white blood count and dividing the product by 100. This number represents the amount of neutrophils that are available for defending the body at the time of the blood test. A normal ANC is generally within the range of 1,800-7,000.

**Acute myeloid leukemia (AML)**, an acute form of leukemia, a malignant disease of the white blood cells affecting *monocytes* or granulocytes. It is characterized by the appearance of immature, abnormal cells in the bone marrow and peripheral blood.

**Anemia**, too few (lack of/not enough) red blood cells (Erythrocytes).

**Antibiotics**, drugs, which specifically kill *bacteria* or prevent their spreading and thereby support neutrophil granulocytes in the defense of bacterial infections.

**Antibodies**, proteins made by a subgroup of white blood cells — the lymphocytes — that are responsible for the body’s defense. Antibodies are normally directed against foreign structures like *bacteria* or *viruses*. However, sometimes they also may be directed (react) against structures and cells of their own body, e.g. in the case of anti-neutrophil antibodies where the antibodies recognize and destroy the patient’s own neutrophils.
Aplastic anemia, a (extreme) deficiency of all types of blood cells (up to a complete absence), representing (caused by) a failure of the bone marrow to produce these cells.

Arthritis, inflammation of joints.

Autoimmune, the immune system fights against the own body.

Autosomal, refers to the genetic information for a special characteristic not based on the sex chromosome and therefore is inherited across gender.

Bacteria, single organism without a nucleus which can cause diseases. However, in every healthy organism harmless bacteria (e.g. bacteria of the intestinal flora) can exists as well.

Bands, juvenile neutrophils. These are usually counted as neutrophils and contribute to the absolute neutrophil count (ANC). They may also be called “stabs” on a differential count.

Basophils, a subgroup of granulocytes, which may increase after splenectomy.

Blood cells, (counted) among them are white blood cells (leucocytes), red blood cells (erythrocytes) and platelets (thrombocytes).

Blood count, analysis of the cellular blood composition.

Bone marrow, the spongy material located in the center of our bones. It is the home of our stem cells, which reproduce to create our blood, including white blood cells, red blood cells, platelets, B- and T-lymphocytes and macrophages.
(BMT), see “hematopoietic stem cell transplantation.”

**CBC (Complete Blood Count)**, a determination of the numbers of all types of cells present in the blood; same as FBC.

**Chemotherapy**, a combination of drugs with partially enormous side effects to treat cancer.

**Chromosomes**, carry all genetic information and are located in the cell nuclei. Changes of the chromosomes may indicate the development of a disease. They are counted and examined by cytogenetic testing.

**Congenital**, innate.

**Cutaneous**, concerning the skin.

**Cytogenetics**, a method by which chromosomes are counted and analyzed under the microscope.

**Cytokine**, small protein that is important for cell signaling, especially for immune cells.

**Differential blood count**, a form of blood count that specifies the number of each type of white blood cell.

**Erythrocytes**, red blood cells (which transport oxygen through the body).

**FBC (Full Blood Count)**, a determination of the numbers of all types of cells present in the blood; same as CBC.

**Fever**, body temperature above 38.5°C.
Filgrastim, the international non-proprietary name for recombinant human G-CSF.

G-CSF, granulocyte colony-stimulating factor, a protein that stimulates the production and function (antibacterial activity) of granulocytes.

G-CSF receptor, a structure on the surface of a cell to which G-CSF binds and thereby information (signals) to the cell on how to proceed (e.g., grow, divide, mature, etc.) is transmitted.

Genetic engineering, a method by which a gene can be changed in structure or reproduced in the laboratory. Examples include gene cloning, production of recombinant proteins (such as G-CSF), and gene therapy.

Granulocyte, a type of leukocyte which includes not only neutrophils, but also eosinophils and basophils. The terms “granulocyte,” “neutrophil,” and “polymorphonuclear leukocyte” are often used interchangeably.

Hematopoiesis, the formation of blood in the bone marrow. Thereby all blood cells emerge/develop from a common precursor cell, the so called hematopoietic stem cell.

Hematopoietic growth factor, a protein stimulating the production and growth of blood cells.

Hematopoietic stem cells, very rare bone marrow or blood cells that have the potential to develop into any type of mature blood cell (e.g., red cells, white cells, platelets). These cells are NOT the same as embryonic stem cells. They are also called pluripotent stem cell.

Hematopoietic stem cell transplantation (HSCT), the transfer of blood-forming stem cells from one individual (the donor) to another (the
recipient), leading to permanent replacement of the recipient’s bone marrow, blood, and immune system with donor cells. The stem cells may come from the donor’s blood or bone marrow. In the latter case, the procedure is termed bone marrow transplantation (BMT).

**Hematuria**, the occurrence of blood in the urine.

**Hepatomegaly**, enlargement of the liver.

**HIV**, human immunodeficiency virus.

**Incidence**, the number of new cases of a certain disease in a certain time period.

**Kostmann syndrome**, a specific type of severe congenital neutropenia with autosomal recessive inheritance, due to mutations in the \( HAXI \) gene.

**Lenograstim**, the international non-proprietary name for one form of G-CSF.

**Leukemia**, a malignant disease of the white blood cells.

**Leukocytes**, a general term for all white blood cells, including granulocytes, monocytes and lymphocytes.

**Lymphocytes**, subgroup of leukocytes which are responsible for the body’s defense against viruses (T lymphocytes) and the production of antibodies (B lymphocytes).

**Metabolic**, refers to the balance between uptake, degradation and utilization of food.
**Metabolic disease**, disorders/illnesses affecting certain digestive and metabolic processes/functions.

**Monocytes**, a subgroup of leukocytes, which eliminate infectious particles and infected cells by eating and digesting them.

**Morphological**, refers to the physical shape and size.

**Myelodysplastic syndrome (MDS)**, a syndrome characterized by decreased blood counts, the appearance of abnormal cells in the bone marrow and changes in the chromosomes of bone marrow cells. MDS can progress to leukemia.

**Myelokathexis**, a very rare form of congenital neutropenia that is characterized by the inability of the neutrophils to leave the bone marrow and enter the blood.

**Neutropenia**, a reduced amount of neutrophil granulocytes in the blood.

**Neutrophils (neutrophil granulocytes)**, a subgroup of granulocytes defending the body against bacteria and fungi.

**Osteopenia**, mildly demineralized bone substance.

**Osteoporosis**, severely demineralized bone substance partially accompanied by fractures.

**Platelets**, a subgroup of blood cells responsible for clotting; also called thrombocytes.

**Pluripotent stem cell**, mother cell of blood formation which produces all other blood cells. They are also called hematopoietic stem cells.
Polymorphonuclear leukocyte or “poly”, a neutrophil with a multi-lobed nucleus, also called a “PMN.” The terms “poly,” “granulocyte,” and “neutrophil” are often used interchangeably.

Promyelocytes, precursors of granulocytes in the bone marrow.

Prophylactic, preventing.

Prophylaxis, any procedure to avoid undesired events e.g. the development of infections.

Proteinuria, the occurrence of protein in the urine.

Psoriasis, a disease characterized by scaly skin.

Rheumatoid arthritis, chronic inflammation of several joints also referred to as polyarthritis.

Segmented neutrophils, mature neutrophils. These are usually counted as neutrophils and contribute to the absolute neutrophil count (ANC).

Splenectomy, surgical removal of the spleen.

Splenomegaly, the enlargement of the spleen.

Sporadic, the new occurrence of a dominant condition in a family in which the condition has never occurred before, caused by a mutation that arises prior to conception, only in the egg or the sperm of a parent.

Stem cells, rare cells found in most tissues, with the abilities both to renew themselves by cell division and to produce a wide range of mature, specialized cell types. See hematopoietic stem cells for the type specific to blood formation.
Subcutaneous, under the skin.

Syndrome, a complex of various disease characteristics.

Thrombocytes, a subgroup of blood cells responsible for clotting which are also referred to as platelets.

Thrombocytopenia, a decreased number of platelets in the blood (<150,000 per mm$^3$).

Ulceration, formations of ulcers.

Vasculitis, inflammation of small blood vessels.

Viral, caused by viruses.

Viruses, smallest organisms which can multiply only inside other cells such as human cells and destroy them there.

WHIM syndrome, a genetic disorder encompassing warts, hypogammaglobulinemia (low levels of antibody in the blood), infections, and myelokathexis (low numbers of leukocytes and retention of neutrophils in the bone marrow).

White blood count, the total number of leukocytes in the blood.

White blood cells (Leukocytes), a subgroup of blood cells consisting of monocytes, granulocytes and lymphocytes which together form the immune system and defend the body against infection.