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UNDERSTANDING SEVERE CHRONIC NEUTROPENIA

A Handbook for Patients and Their Families

Written for the

Severe Chronic Neutropenia International Registry

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Introduction

Severe chronic neutropenia (SCN) is the name given to a group of conditions in which neutropenia is the primary problem. The severity and symptoms of the 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 for it. We hope that you find it useful in helping 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 go back and ask questions of 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 update your information about neutropenia through websites sponsored by the Severe Chronic Neutropenia International Registry (termed "SCNIR" or "Registry" in this document, http://depts.washington.edu/registry/) and the National Neutropenia Network (NNN, http://neutropenianet.org/) or through reading research papers available at Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/).

The staff and Advisory Board members of the SCNIR wrote 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. 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. 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 to 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 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 a 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 and small nourishing blood vessels. The medical term for blood cell formation is hematopoiesis (see Figure 1).

There are three basic types of blood cells:

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

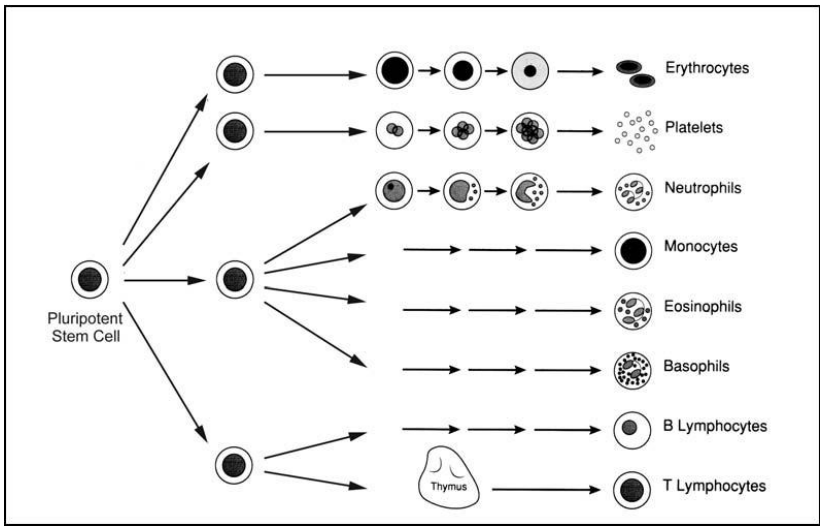

Figure 1. *All types of blood cells are derived from one single 'mother cell', the pluripotent hematopoietic stem cell. "Pluripotent" means the cell can produce many different cell types, but not all cells and tissues, as would an embryonic stem cell.*

The growth and development of the blood is carefully controlled in the bone marrow to produce the correct number of each type of cell to keep the body healthy. About 3 million red and 120,000 white blood cells are produced every second. The mature cells leave the bone marrow and 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).

All blood cells eventually die but their life spans vary amongst the different types of cells. Red blood cells live for about 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 in the blood is too low. Neutrophils are very important in defending the body against bacterial infections (see Figure 2) and therefore, a patient with too few neutrophils is more susceptible to bacterial infections. Neutropenia can occur for different reasons. Patients who have cancer may become neutropenic because of the chemotherapy they receive, sometimes neutropenia occurs after a viral infection. Some people are born with neutropenia, but in some cases the reasons are not known.

The level of neutropenia may vary considerably. In general, the blood of healthy adults contains about 1500 to 7000 neutrophils per mm^3 (1.500 – 7.000 x 10^9/l). In children under 6 years of age the neutrophil count may be lower. To evaluate neutropenia in a child, it is important to compare the child's neutrophil counts to normal neutrophil counts of children the same age. The severity of neutropenia generally depends on the absolute neutrophil count (ANC) and is described as follows:

Mild neutropenia, when the ANC falls below a lower limit of 1500 per mm^3 (1.500 x 10^9/l), but remains higher than 1000 per mm^3 (1.000 x 10^9/l).

Moderate neutropenia, when the ANC falls between 500 per mm^3 and 1000 per mm^3 (0.500 x 10^9/l - 1.000 x 10^9/l).

Severe neutropenia, when the ANC falls below 500 per mm^3 (0.500 x 10^9/l).

Very severe neutropenia (sometimes termed "agranulocytosis"), when the ANC falls below 200 per mm^3 (0.200 x 10^9/l).

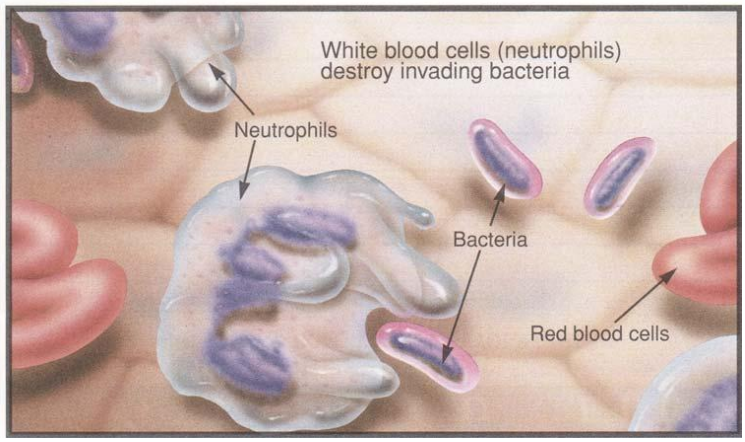

Figure 2. *An artist's view of neutrophils attacking bacteria in the bloodstream.*

The duration of the neutropenia may be short lived, in which case, the patient is described as suffering from acute neutropenia. However, if a patient has neutropenia for a longer period, i.e., greater than three months, the patient is considered to have chronic neutropenia.

The severity of symptoms usually correlates with the level of neutropenia. The lower the neutrophil count, the greater the risk of infection. This risk increases if low neutrophil counts persist for more than three days. Common types of mild infection include otitis media; tonsillitis; sore throat; mouth ulcers; gum infection and skin abscesses. Serious infections include pneumonia, peritonitis, and bloodstream infection (sepsis). Any fever (body temperature above 38.5°C/101.3°F) must be taken very seriously and the patient's nurse or physician should be informed.

Severe neutropenia can lead to serious problems, which require prompt care and attention as the patient could potentially develop a bacterial, fungal or mixed infection at any time. These infections can be life threatening when the patient has persistent severe neutropenia. It is important that the patient sees a doctor as soon as possible and be treated with medications to fight the infection (such as antibiotics).

Overview:
Diagnosis & Treatment of Severe Chronic Neutropenia

When a bone marrow sample is taken for diagnostic purposes, the cells are looked at under the microscope (see Figure 3) and often are used for other investigations, such as *cytogenetics*. If possible, a sample is sent to the SCNIR bone marrow cell bank to be used for research.

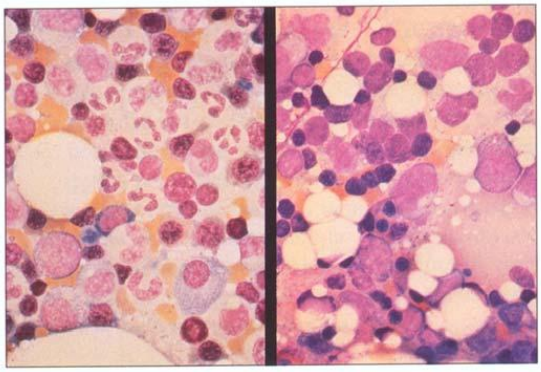

Figure 3. *A typical bone marrow of a patient with severe congenital neutropenia showing the absence of mature neutrophils (right) compared to the bone marrow of a healthy individual with neutrophils at all stages of maturation (left).*

With the cytogenetic evaluation, the chromosomes of the bone marrow are counted and studied for structural alterations. Most of the time, in the majority of patients with neutropenia, this test is completely normal. Changes in the chromosomes of cells can be harmless, but in some cases changes could indicate a possible progression towards leukemia (see Figure 4). This is the most important reason for routine annual bone marrow investigations.

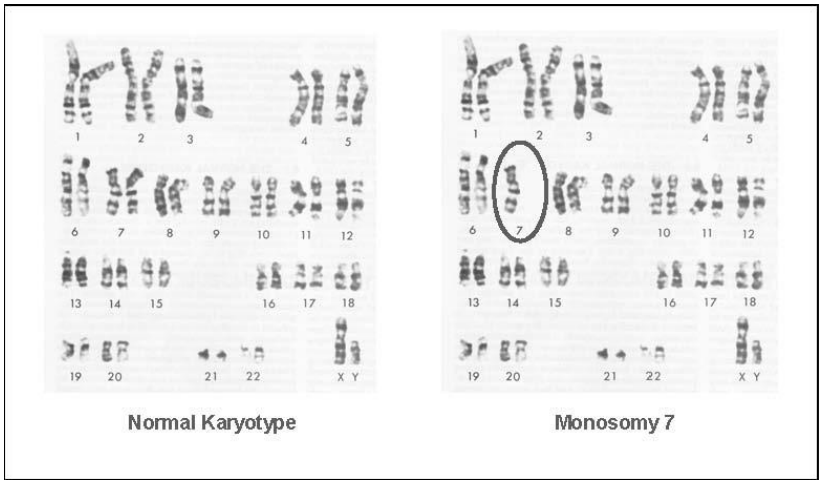

Figure 4. *Each human cell (except for oocytes and sperms) contains two sets of 22 chromosomes and two additional sex chromosomes (females: XX, males: XY) as shown on the left side of this figure. Pre-leukemic changes may be represented e.g. by the loss of chromosome 7 as shown on the right panel of the figure, above.*

As soon as congenital neutropenia is diagnosed, most patients begin treatment with a hematopoietic growth factor called G-CSF (also known as filgrastim or lenograstim). Clinical trials of G-CSF treatment began at Amgen in 1987. This treatment resulted in a dramatic increase in the neutrophil count, leading to improved life expectancy and quality of life in these patients. As soon as the neutrophil counts have risen and stabilized, the patient can lead a normal life, including participation in school and sports. Before G-CSF was available, most patients died from severe bacterial infections within their first few years of life because no other treatment was able to correct their neutropenia adequately. Even antibiotic therapy could only prolong the life of these patients for a short while, because both neutrophils and antibiotics are necessary to overcome bacterial infections.

G-CSF is a natural cytokine produced by the human body. A cytokine is a protein produced by cells, which is essential for the regulation of other cells. Patients with congenital neutropenia also produce G-CSF, but not in amounts adequate to correct the severe neutropenia in SCN. The lower the neutrophil count, the greater the risk of infection. Occurrence of severe bacterial infections is strongly correlated with low neutrophil counts. In most patients treated with G-CSF, bacterial infections resolve and recur less frequently once the neutrophil count stabilizes above 1000 neutrophils per mm^3 (1.000 x 10^9/l). Individuals vary, some fight off infection with a lower neutrophil count, and others need a higher count.

The response to G-CSF treatment also varies in congenital neutropenia patients. This explains the wide variation in the dose (amount) of G-CSF among the congenital neutropenia population. For more information regarding G-CSF see Treatment for severe chronic neutropenia. A very small subgroup of patients with congenital neutropenia do not respond even to very high doses of G-CSF. Patients who do not respond to G-CSF within fourteen days or require doses of more than 10 micrograms/kilogram (mcg/kg) may be evaluated for possible hematopoietic stem cell transplantation (discussed below).

Risk of Myelodysplastic Syndrome and Leukemia

During the last 20 years, data have been collected on more than 1100 patients with chronic neutropenia. These data indicate that patients who have severe congenital neutropenia have an increased risk of developing myelodysplastic syndrome (MDS) or leukemia, compared with healthy individuals. The risk appears to rise during the first 10 years on G-CSF therapy, then stabilizes but remains high, reaching around 20% after 15 years on treatment. In general, those who require high doses of G-CSF and still

have low neutrophil counts (poor responders) have the highest risk, whereas those who maintain excellent neutrophil counts on lower doses of G-CSF have a risk of MDS/leukemia below that of poor responders, but still higher than the normal population. It is still not clear whether G-CSF permits survival to an age at which leukemia occurs due to the underlying bone marrow disorder or if there is an effect of G-CSF to promote the development of leukemia. In the era before G-CSF, patients with severe congenital neutropenia who survived past infancy also developed MDS and leukemia. The risk of leukemia is also high in other congenital diseases affecting blood cell formation (termed the inherited bone marrow failure syndromes). In any case, for most patients, the risk of infection without G-CSF treatment outweighs the risk of eventual leukemia. In addition, hematopoietic stem cell transplantation, the alternative to G-CSF treatment, has significant risk.

Importantly, patients with cyclic neutropenia and acquired (e.g. idiopathic or autoimmune) neutropenia do NOT appear to be at risk for MDS or leukemia, whether or not they receive G-CSF therapy.

The SCNIR recommends that all patients with all types of severe congenital neutropenia, except cyclic neutropenia, have a bone marrow examination and cytogenetic analysis on a yearly basis. A bone marrow examination is also recommended any time there is an apparent failure of G-CSF treatment or a worrisome change in blood counts. Transplantation should be considered if the bone marrow or chromosome pattern shows abnormalities indicating conversion to MDS or leukemia.

Risk of Osteopenia/Osteoporosis

Patients with chronic neutropenia on G-CSF therapy have in increased risk low bone density (osteopenia), which can lead to osteoporosis (more serious thinning of the bones). Osteoporosis may occur even in childhood in patients with severe chronic neutropenia. The risk of abnormal bone density tends to increase with G-CSF therapy, but it is still not clear whether this trend is due to the treatment or the underlying bone marrow disorder. However, very few patients actually experience clinical problems, such as pain and/or fractures due to their osteoporosis. As neither the exact cause nor the medical implications of osteoporosis are fully known, further research is underway on this problem. The SCNIR recommends monitoring of patients' bone density on a regular basis with a dexascan followed by referral to an endocrinologist if the dexascan is abnormal.

Types of Severe Chronic Neutropenia

Severe chronic neutropenia can exist from birth (congenital neutropenia) or can occur at any time through life (acquired neutropenia). It may develop by itself or as an accompanying symptom of a different underlying disease. The following list gives examples of the different types of chronic neutropenias.

Neutropenias present at birth:

Severe congenital neutropenia (includes Kostmann syndrome)
Cyclic neutropenia
Shwachman-Diamond syndrome

Metabolic diseases associated with neutropenia:

Glycogen-storage disease type 1b
Severe congenital neutropenia due to G6PC3 mutations
Barth syndrome

Immune disorders associated with neutropenia:

Common variable immunodeficiency
Myelokathexis/WHIM syndrome
Wiscott-Aldrich syndrome

Neutropenias that are acquired during life:

Idiopathic neutropenia
Autoimmune neutropenia

Severe Congenital Neutropenia

Severe congenital neutropenia is a rare type of neutropenia that is present at birth. It is an inherited disease and, therefore, more than one family member can be affected, but sporadic occurrence with only one patient in a family is also possible. One specific genetic form is termed "Kostmann syndrome," but the name is also used at times as a general term for severe congenital neutropenia. Prenatal genetic diagnosis may be available in families in which the specific gene mutation has been identified.

Congenital neutropenia is usually very severe, and neutrophils are often completely absent in the blood of these patients at the time of diagnosis. Patients who are diagnosed with congenital neutropenia usually show a "maturation arrest" (see Figure 5) in the early stages of neutrophil development in the bone marrow. This means that their neutrophils rarely fully mature into the cells that are capable of fighting infections.

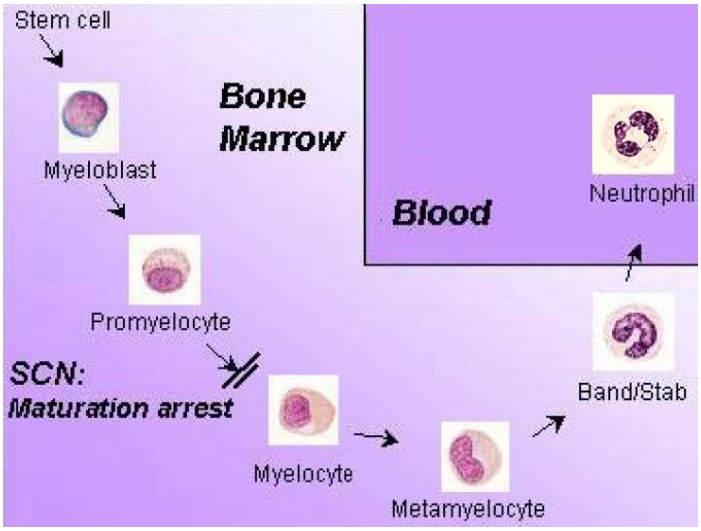

Figure 5. *In healthy individuals, the maturation of neutrophilic granulocytes leads to segmented neutrophils, which leave the bone marrow and enter the blood. In congenital neutropenia patients, the maturation pathway is blocked at the stage of early precursor cells, the promyelocytes.*

These patients suffer from severe bacterial infections, such as omphalitis (infection of the umbilical stump), pneumonia, skin abscesses or otitis media (ear infections) during their first few months of life. Therefore, in most patients congenital neutropenia is diagnosed during infancy. A blood test and a bone marrow sample are required in order to obtain a correct diagnosis.

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 cycle length of 21 days. These cycles vary from patient to patient. Some individuals remain neutropenic during the whole cycle while others have low neutrophil counts for only a few days and normal blood counts during the rest of the cycle (see Figure 6). 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 with 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 three times per week over six 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 per mm^3 [0.200 x 10^9/l]) every three weeks with some symptoms almost every cycle, but significant infections (e.g., pneumonia or bloodstream infection) 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 marrow changes during the cycle, from normal appearance to that of severe maturation arrest of neutrophil production, and then back again to normal.

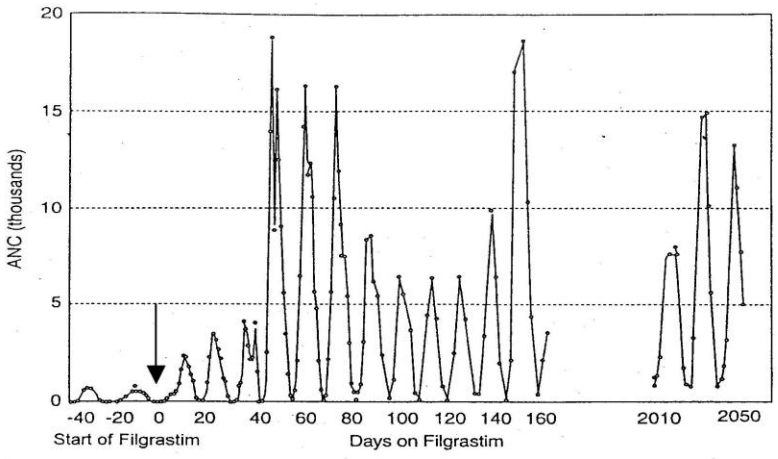

Figure 6. *The absolute number of neutrophils in the blood of cyclic neutropenia patients cycles according to a typical pattern. Under G-CSF (filgrastim) therapy, the cycling is still present but the cycle length is shortened and the duration and depth of the neutropenic phase is decreased.*

Other blood cells, such as platelets or red cells, can also show oscillations with a cyclical pattern. Cyclic neutropenia can occur sporadically, but there are families in which cyclic neutropenia is inherited with one parent and more than one child affected. Patients with cyclic neutropenia benefit from G-CSF treatment, usually requiring lower doses than those used for severe congenital neutropenia. They appear to be at little or no risk of developing MDS or leukemia.

Shwachman-Diamond Syndrome

Patients who present with increased volume and frequency of fatty stools need testing for pancreatic function to rule out Shwachman-Diamond syndrome (SDS).

SDS is an inherited (*autosomal recessive*) condition with multisystem abnormalities including pancreatic insufficiency (problems with digestion of fats in the diet resulting in large volume fatty stools), neutropenia, and short stature. At the time of diagnosis the features of SDS are extremely variable. The vast majority of patients are diagnosed in infancy, with symptoms of fatty stools and poor growth, with or without hematological abnormalities (including neutropenia). Other less common features can also be present at diagnosis. These include (extreme) short stature, skeletal abnormalities, and marked liver enlargement. SDS must be considered even if clinical symptoms of pancreatic insufficiency are absent because a significant percentage of patients do not have problems with digestion, or their symptoms may have resolved prior to the recognition of neutropenia.

If neutropenia becomes severe, 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 for congenital neutropenia, patients with SDS have also an increased risk in developing leukemia and 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 metabolic disorder, which affects the glucose (sugar) metabolism. The liver, spleen and other tissues accumulate *glycogen*. Patients present with an enlarged liver and spleen, failure to thrive, kidney problems, hypoglycemia (low blood sugar) and 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. Patients respond to treatment with G-CSF not only with an increase in ANC but also with improvement of the activity of their neutrophils.

Barth syndrome is a very rare metabolic disorder that includes not only neutropenia, which may be cyclic, but also heart muscle weakness (cardiomyopathy) and growth delay. For more information, visit http://www.barthsyndrome.org.

Idiopathic Neutropenia

The term 'idiopathic neutropenia' describes various types of neutropenia that 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 long-term treatment. There is no evidence for any increased risk of MDS or leukemia in patients with idiopathic neutropenia, whether or not they receive G-CSF therapy. Likely the causes of idiopathic neutropenia are multifactorial and may include autoimmune, genetic, and physiologic causes.

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, is the most common cause for neutropenia of this age group. Although these infants often have very low absolute neutrophil counts, they usually do not suffer from severe bacterial infections.

Anti-neutrophil antibodies may be detectable by immunological blood tests that can be performed in specialized laboratories, but the absence of a positive test to these antibodies does not rule out the diagnosis of autoimmune neutropenia, nor does a positive test rule out congenital neutropenia. Patients should be kept under medical care, but may not necessarily require treatment with antibiotics or G-CSF.

Depending on the frequency of infections and the neutrophil counts, prophylaxis with an oral antibiotic may be considered by the treating physician. For the few children who develop severe infections or have significant impairment of life style (e.g., frequent visits to emergency rooms),

treatment with G-CSF is almost always effective. In most children the blood counts normalize by age 3-5 years.

Autoimmune neutropenia is also seen in adults, predominantly in women. The adult form of autoimmune neutropenia is less likely to resolve spontaneously and more likely to be associated with other autoimmune disorders.

There is no evidence for any increased risk of MDS or leukemia in patients with autoimmune neutropenia, whether or not they receive G-CSF therapy.

Other Conditions Associated with Neutropenia

There are a number of other conditions that include neutropenia as part of the symptoms. Depending on the nature of the main condition the way the neutropenia is managed may differ from the treatment of 'pure' SCN described. The main conditions that may include neutropenia are:

Severe acquired aplastic anemia
Viral illnesses
Post chemotherapy or radiotherapy
Other drug-induced situations
Fanconi anemia

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 and more information about diseases associated with neutropenia is being discovered all the time.

Genetics of Severe Congenital Neutropenia

Recent research, much of it based on SCNIR data and materials, has identified the genetic basis of many of the inherited forms of severe chronic neutropenia, as well as genetic alterations responsible for some of the multifaceted syndromes accompanied by neutropenia. The diagnosis of these disorders, which is generally based on clinical and laboratory features, may now be supplemented by genetic testing. Under some circumstances, these tests also can be applied to prenatal diagnosis.

The classification of primary neutropenias refers to disorders of neutrophil production, including cyclic neutropenia and severe congenital neutropenia. Cyclic neutropenia is inherited in an *autosomal dominant* fashion. It can occur sporadically as well. Both *sporadic* and autosomal dominant cyclic neutropenia derived from mutations in the ELANE gene (formerly termed ELA2) encoding the protein neutrophil elastase (Table 1). Severe congenital neutropenia can occur sporadically, in an autosomal dominant fashion, or as an autosomal recessive disorder (Kostmann syndrome). Mutations in the *ELA2* gene are responsible for 60% of severe congenital neutropenia cases (Table 1). Additionally, very rare cases of autosomal dominant severe congenital neutropenia can arise from mutations in the genes *GFI1, PRDM5,* or *PFAAP5*. The autosomal recessive form of severe congenital neutropenia is associated with mutations in the *HAX1* gene (Kostmann syndrome) or *G6PC3* gene (a very rare syndrome that also includes heart, urogenital, and skin abnormalities). It is important to note that autosomal dominant disorders, even when occurring sporadically, have a 50% chance of being passed on to the children of an affected individual. Autosomal recessive disorders have a 25% chance of occurring in the siblings of an affected patient, but only a very remote chance of being passed on to the next generation. Healthy siblings of affected patients documented to have autosomal dominant neutropenia do not run the risk of transmitting neutropenia to their children.

Genetic Classification of Neutropenia Syndromes		
Disorder	**Inheritance**	**Gene(s)**
Disorder of neutrophil production		
Cyclic neutropenia	autosomal dominant	*ELA2*
Severe congenital neutropenia	autosomal dominant	*ELA2*, other rare genes
Kostmann syndrome	autosomal recessive	*HAX1*
Disorder of the nucleus		
Shwachman-Diamond syndrome	autosomal recessive	*SBDS*
Disorders of metabolism		
Glycogen storage disease, Type 1b	autosomal recessive	*G6PT1*
Barth syndrome	X-linked recessive	*TAZ1*
Disorder of Immune Function		
Myelokathexis (WHIM syndrome)	autosomal dominant	*CXCR4*

Much rarer causes of neutropenia include disorders affecting the nucleus or metabolism of neutrophil-producing cells, or interfering with immune function. In Shwachman-Diamond syndrome (see separate section above/below) around 90% of patients who meet the clinical criteria for this syndrome harbor mutations in the *SBDS* (Shwachman-Bodian-Diamond syndrome) gene, which is inherited in an autosomal recessive fashion. Another disorder of neutrophil production, glycogen storage disease Type 1b is associated with the abnormalities in the metabolism of neutrophil precursor cells. It is inherited in an autosomal recessive fashion and is associated with mutations in the gene, *G6PT1*. Barth syndrome, another rare disorder of metabolism, is inherited as an X-linked recessive disorder, which appears in males. In this inheritance pattern, there is a 50% chance of the same disease in a patient's brothers. The children of affected men cannot have the disease, but their daughters carry the gene and have a 50% chance of transmitting the disorder to their sons. Among the immune disorders, myelokathexis (part of the *WHIM* syndrome) is transmitted as an autosomal dominant disorder.

The SCNIR office can provide advice on where genetic counseling and testing can be obtained.

Diagnostic Tests Used in Severe Chronic Neutropenia

When a diagnosis of neutropenia is suspected (e.g., with recurrent infections which may occur on a cyclical basis) physicians will begin by taking a Complete Blood Count/Full Blood Count and proceed to further tests if necessary (Complete Blood Count (CBC) or Full Blood Count (FBC), is the same thing and these terms are interchangeable). These examinations will be extended to include the bone marrow of the patient. The most important investigations performed are explained below.

Blood Count Monitoring

As already mentioned, the first investigation on suspicion of neutropenia is a CBC/FBC. By this procedure the neutrophil count is measured. If the neutrophil count is low it is normal 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 is normal but at other times it is very low, the physician may suspect cyclic neutropenia. To confirm the diagnosis the physician will arrange for blood samples (CBC/FBC) to be taken three times per week for at least six weeks to see whether there is a regular cyclical pattern of neutrophil counts.

Other Blood Tests

The physician will also do a blood test to exclude autoimmune neutropenia by testing for antibodies (see section regarding autoimmune neutropenia).

Bone Marrow Aspiration/Biopsy

If the patient's blood tests indicate neutropenia, then it is important to do a bone marrow examination to confirm the diagnosis by looking at the marrow cells under the microscope (see Figure 4).

Bone marrow cells are usually taken from the large pelvic bone, the ilium, or, sometimes also from the flat breastbone, the sternum. This is usually done with the patient asleep under general anesthetic or under local anesthetic with sedation. The actual technique may vary between treating centers. Your physician will explain exactly how the procedure will be done for you.

There are two different methods to examine bone marrow. The first is a bone marrow aspirate where marrow cells can be taken out like taking a blood sample from a vein but this time from the middle of the bone. In the second method, bone marrow biopsy, a small piece of bone marrow is taken and processed differently, to look at the architecture of the marrow structure.

Cytogenetic Evaluation and Molecular Testing

As mentioned previously, it is important to monitor the cytogenetics of the marrow cells, as changes in the chromosome pattern may develop before any abnormalities in the appearance of bone marrow cells.

There are additional techniques by which some cytogenetic changes can be monitored; your physician will explain these to you.

SCN is a very rare disorder. Some treating centers are actively involved in research of SCN and may suggest other investigations.

Investigations in Other Conditions

To be certain about the diagnosis of conditions that are not limited to the blood system (e.g., Shwachman-Diamond syndrome, glycogen storage disease type 1b and others) investigations beyond blood tests may be necessary. Your physician will explain what further tests are required. Sometimes this may involve visits with other specialists.

Treatment for Severe Chronic Neutropenia

The treatments that have been tried or are being used in the management of congenital, cyclic and idiopathic neutropenia include:

Granulocyte-colony stimulating factor (G-CSF)

Hematopoietic stem cell transplant (HSCT; also called bone marrow transplant)

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 weaken other parts of the immune system.

Supportive care, discussed below

Treatments prescribed by your physician are extremely important to decrease the potential for infection. Good nutrition and hygiene (including good dental hygiene) are also very important. Nutritional treatments will not however 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 and potential risks.

Granulocyte-Colony Stimulating Factor (G-CSF, Neupogen®)

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 of, and enhances the activity of, mature neutrophils thus improving their bacteria-killing function. It acts via a receptor localized on granulocytes that binds the G-CSF to the cell and produces a signal to tell the cell to mature, to divide or to enhance function (see Figure 3). SCN patients produce their own G-CSF, but much larger (treatment) doses of G-CSF are required to correct the neutrophil count.

The dose and frequency of injection of G-CSF required to increase and maintain the neutrophil count to 1000 per mm^3 (1.000 x 10^9/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 is sufficient. But some patients need very high doses, even up to 120/mcg/kg/day (potentially injected more than once per day). Others need very low doses, as low as 0.01 mcg/kg/day. Some patients may require injections less often than daily, but short-term adjustments may be necessary if infection occurs. Treatment less often than every two or three days is rarely effective.

G-CSF is usually administered by a subcutaneous injection (i.e. an injection just under the skin). Recommended sites include the abdomen below the naval, upper outer arms, and upper outer thighs (Figure 7). It is possible to self-administer G-CSF and this should be encouraged as it promotes a sense of independence 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 not usually painful but, 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 report bone or muscle pain and splenomegaly. Other side effects are infrequent but a few patients have experienced thrombocytopenia, injection site reactions, rash, enlarged liver, joint pain,

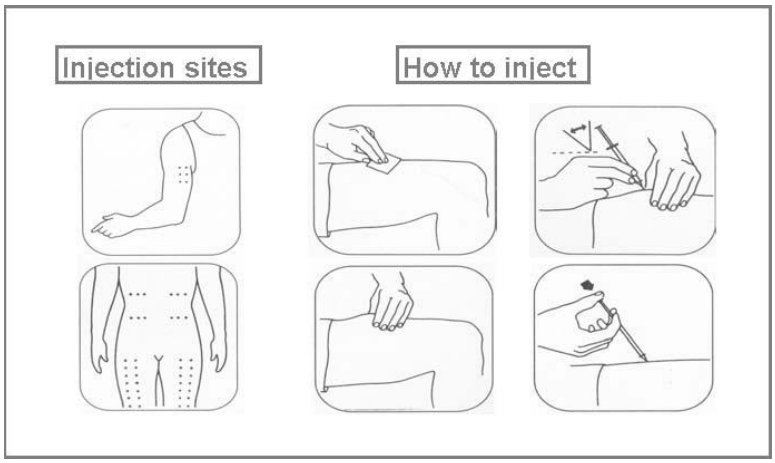

Figure 7. *Where and how to apply G-CSF.*

osteoporosis, rash, blood or protein in the urine, hair loss and exacerbation of some pre-existing skin disorders (e.g., psoriasis). If these or other side effects occur, the patient's doctor should be notified. In addition, cytogenetic abnormalities, transformation to myelodysplasia (MDS) and leukemia have been observed in patients with congenital neutropenia treated with G-CSF (this issue is discussed in detail above).

Hematopoietic Stem Cell Transplant

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. Due to the higher risk of MDS and leukemia in SCN with a poor response to high doses of G-CSF (see Risk of MDS/Leukemia), some individuals in this group may also be considered for HSCT. Transplantation is a very intensive procedure, carrying serious risks and is therefore not recommended as first choice treatment. It is important for the patient and physician to discuss in detail the risks and benefits of this procedure.

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 at increasing neutrophil counts in the blood. Steroids work by encouraging 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 and they may decrease the function of neutrophils and the number of other types of white cells, thus increasing the risk of infection. In general, steroids have not proven useful for patients with SCN, except for some patients with neutropenia associated with lupus or other chronic rheumatologic conditions. In addition to the unwanted side effects of increasing the risk of infection, long-term use of steroids has many other side effects, e.g., it may induce the development of diabetes mellitus.

White cell transfusions:
White blood cell transfusions are rarely used. They are generally reserved for severe life-threatening infections. The replacement of neutrophils by transfusion is not feasible in the long term for various reasons. The collection of these cells is quite difficult, the mature neutrophil has quite a short life span and the cell cannot be stored for more than a few hours. Even more than with other blood products, there are also risks of severe reactions to the transfusion.

Supportive Treatment

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

Mouth care: this should include regular dental checkups. 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 that allows them to make normal antibodies protecting from the devastating effects of viral illnesses. Therefore all routine immunizations according to the standard vaccination schedule of your country are recommended. Influenza vaccine should also be administered if recommended for the patient's age group.

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.

Oral prophylaxis: antibiotics/antifungals, either oral or intravenous, may be given to SCN patients but this is very much based on individual physician choice.

Prompt contact of physician/hospital/clinic: it is important to have these contact telephone numbers easily accessible.

Foreign travel: concerns should be raised with your physician, as special precautions, emergencies and contact telephone numbers need discussion. A list of the neutropenia experts in different European countries cooperating with the SCNIR is located at the website http://www.bmfs.de/

Long Term Management of Severe Chronic Neutropenia

The key issue in the treatment of SCN is "normalization of life" and the promotion of a 'normal life' for you. This includes schooling, vacations, family life and social life. Administering G-CSF allows a neutropenic patient to continue daily life tasks without the risk of dangerously low levels of neutrophils.

A CBC/FBC evaluation gives the physician the information needed to monitor your ANC. Monitoring the ANC alerts the physician to the need to adjust the G-CSF dosing.

When G-CSF treatment is initiated, your doctor will follow your ANC closely, generally for the first 4 to 10 weeks to assure that the dose of G-CSF is correct for you. The Registry suggests that when the dose has been stabilized, severe congenital neutropenia patients should still be monitored with a monthly CBC/FBC. For patients on a daily administration of G-CSF, blood should be drawn approximately 18 hours after dosing. Patients taking G-CSF on a less frequent program should have the CBC/FBC done just prior to the next administration of the medication. This allows the physician to monitor the ANC at its lowest point. (See neutropenia health tips on the website, check out CBCs, nice table, may want to include)

Bone Marrow Monitoring

Bone marrow aspirate and biopsy procedures are done to help the physician diagnose the patient's medical condition. The bone marrow evaluation will help confirm if the patient has congenital neutropenia or another form of neutropenia. After the diagnosis is confirmed, the Registry suggests that patients with congenital neutropenia be followed on a yearly basis with bone marrow and cytogenetic evaluations to monitor for changes in their bone marrow. Early detection of MDS or leukemia through bone marrow monitoring can lead to more successful therapy.

SCN patients with types of neutropenia other than congenital neutropenia (such as cyclic, idiopathic, or autoimmune) may have annual bone marrow testing at the discretion of their physician.

Pregnancy

The SCNIR collects information on SCN patients and pregnancy; however, the number of pregnancies reported to date is relatively small and thus little information is known about the potential effects of G-CSF during pregnancy. Therefore, the use of G-CSF during pregnancy should be evaluated on an individual basis with your primary physician, who can weigh the currently-known risks and benefits of the treatment in the context of your individual situation. Because the safety of G-CSF administration during pregnancy is not yet established, the current recommendation given by the experts of the SCNIR is that if possible, G-CSF should be avoided or minimized during the first trimester. You should discuss this issue with your physician well in advance of any decisions regarding pregnancy. It will then be possible for your physician to review the current pregnancy data with you and develop a plan for G-CSF dosing.

Psychosocial Issues

Family dynamics, school and employment all can be affected by the increased stress caused by the chronic illness of a family member. Families and patients with SCN may experience similar stresses to those found in families with a family member with diabetes, epilepsy, cystic fibrosis, or other long-term conditions. Children with SCN will experience the normal milestones of childhood along with the added stress caused by having a chronic condition.

After the diagnosis of SCN the patient and family may experience the common feelings of confusion, bewilderment and possibly anger. 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. 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.

All pre-school children's developmental milestones include the mastery of their environment. Children with SCN need to be involved in their health care as is appropriate for their age. This may include learning to clean cuts and scrapes, proper hand washing, and helping with the administration of the G-CSF. At this age it may be beneficial for a child to be given a doll to care for that also is 'neutropenic' allowing the child to act as the doll's caregiver. The treated SCN child may want to act out giving the doll medication. This allows the child to act out the frustrations he/she is feeling regarding the neutropenia and to begin the process of learning necessary coping mechanisms.

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. The SCN child

will need all caregivers (such as school teachers, school nurses, day-care providers, coaches, etc.) to understand SCN. The SCNIR website has letters explaining SCN that you can share with providers.

Adolescence is a difficult time for most children. Children with SCN will realize, often for the first time that they are different from their peers. This may be the first time the child understands that he/she will have SCN for the rest of their life. The adolescent may feel that SCN affects school or relationships with peers. It is not uncommon for the adolescent to respond with denial and/or resentment of their condition. They may develop behaviors such as not caring for skin infections, lack of good oral hygiene or stopping the administration of the G-CSF.

At this stage the adolescent is struggling to maintain a positive self-image. The child may struggle against anything that appears to label them negatively. It is important for the parent to be alert to signs of change in habits or patterns that might indicate signs of depression or unusual anger (such as decreased interest in school or extreme behavior). Parents need to trust their intuition and knowledge of the child's normal behavior. If a parent observes concerning changes in the adolescent's behavior, they should contact the child's primary health care provider to discuss their concerns.

The Severe Chronic Neutropenia International Registry

The Severe Chronic Neutropenia International Registry (SCNIR) was established in 1994 to monitor the clinical course, treatment, and disease outcomes in patients with severe chronic neutropenia (SCN). The Registry has the largest collection of long-term data on patients with this condition in the world. Participation in the Registry benefits patients, their families and the physicians who treat them by providing the most up-to-date information on the natural history of SCN and its treatment options.

Patients qualify for the Registry if:

Their ANCs are under 500 per mm^3 (0.500 X 10^9/L) on at least three occasions in the three months prior to applying for the Registry (if currently treated, three ANC's under 500 per mm^3 [0.500 X 10^9/L] prior to the start of G-CSF therapy) with the exception of patients with Shwachman-Diamond syndrome, glyogen-storage disease type 1b and Barth syndrome who are enrolled with higher ANC's or even no neutropenia at all.

There is a history of recurrent infections.

Patients do not qualify for the Registry if:

Their neutropenia is known to be drug-induced.

The patient has any one of the following conditions:

- Thrombocytopenia (SDS and GSD-1b patients are an exception to this exclusion)
- Myelodysplastic syndrome
- Aplastic anemia
- HIV positive
- Known immune diseases such as rheumatoid arthritis

The patient has had chemotherapy for cancer within the past 5 years.

For patients qualifying for the Registry the following basic examinations are required:

A bone marrow evaluation has been completed that confirms the diagnosis of SCN.

A cytogenetic evaluation has been completed, if G-CSF treatment has been considered or initiated.

The patient has signed a formal consent to allow the anonymous use of his/her data.

The objectives of the SCNIR are to:

Document the clinical course of SCN and monitor clinically significant changes e.g., primary treatment response over time and long-term safety.

Study the incidence and/or outcome of the following previously identified adverse events: osteoporosis, splenomegaly, vasculitis, thrombocytopenia, cytogenetic abnormalities, myelodysplastic syndrome, and leukemia.

Establish a physician network to increase the understanding of SCN.

Establish a demographic database to allow for current and future research.

Collect bone marrow samples of patients at different time points for current and future research.

The SCNIR Advisory Board of expert physicians/hematologists list can be found on the SCNIR web site: http://depts.washington.edu/registry/

A panel of European physicians/hematologists called the Local Liaison Physicians located throughout the European countries can be found on the web site http://www.scner.de/eu_seiten/eu_seite.htm

Information concerning the SCNIR can be obtained from the web site:
http://depts.washington.edu/registry/

In the USA

Severe Chronic Neutropenia International Registry
University of Washington, Seattle
Phone +1(206)543-9749* or
(800)726-4463 (inside the U.S.)
FAX +1(206)543-3668*

In Europe

Severe Chronic Neutropenia International Registry
Medizinische Hochschule Hannover
Kinderklinik
D-30623 Hannover, Germany
Phone +49 (511) 557105*
FAX +49 (511) 557106*

Severe Chronic Neutropenia International Registry Web Sites

United States
http://depts.washington.edu/registry/

Germany
http://www.scner.de/

Support Groups

Support groups can provide assistance with linking families to others who have a family member with SCN. These contacts can help alleviate the alienation families often feel when one of their members is chronically ill.

USA

National Neutropenia Network
Lee Reeves
http://neutropenianet.org/
Phone (517-294-0736)

Schwachman-Diamond Syndrome Foundation
Lorna Stevens
Phone (877) 825-7373 (inside the U.S. only)

Barth Foundation
Linda Stundis
http://www.barthsyndrome.org
Phone: (617) 469-6769

Canada

Neutropenia Support Association Inc.
http://www.neutropenia.ca/
Phone (800) 663-8876

Europe

Interessengemeinschaft Neutropenie Hannover
Phone +49 (4441) 911133*
*The + preceding the country code represents the local predial code for international calls.

Frequently Asked Questions and Answers

Why does my child have SCN?

Nobody truly knows how and why SCN develops. It is often, but not always, genetically inherited.

Cyclic neutropenia and most cases of congenital neutropenia are inherited in an autosomal dominant manner. This is where one parent actually suffered to some extent from the condition himself or herself due to a gene that was 'dominant' over its partner gene. There is a 50% possibility that other children in the family could be affected and that your child will pass the disorder onto his/her children.

Rare congenital neutropenia cases with a mutation in the *HAX1* gene (Kostmann syndrome) are inherited as an autosomal recessive disorder. This means that the affected patient's parents are carriers of the gene responsible for the disorder, and both passed that gene to their child. The only way your child can pass the disorder on to his/her children is if he/she married somebody else with a carrier gene.

However, in all subtypes of inherited neutropenia exceptions to the above mentioned pathway are possible, e.g., that in some cases the disease can occur for the first time in a family without having a parent carrying the gene.

Autoimmune and idiopathic neutropenia are not inherited and are very unlikely to be passed on to future children. Autoimmune neutropenia may be associated with other autoimmune disorders, for which your physician may wish to perform additional testing.

Will my child with chronic neutropenia develop normally, especially in their growth and development?

Children with chronic neutropenias develop in the usual way. However, some children with congenital neutropenia may tend to be smaller than individuals with other chronic neutropenias or those without neutropenia.

My child is due 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) and all routine vaccinations are recommended to be given at the standard time intervals. Your physician should discuss any limitations based on your child's diagnosis.

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 over the doctor did treat him with antibiotics. My doctor told me the difference was that flu was a different type of infection in which antibiotics would not be successful. I am now extremely confused as to what type of infections I should be looking out for. Can you please explain?

Neutrophils are the most important cells against bacterial and fungal infections. Your child has a reduced number of neutrophils and hence is at greater risk of developing bacterial infections. Skin cuts, abrasions, ulcers etc., are at risk of becoming infected by bacteria. 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.

What is the life expectancy of a child with chronic neutropenia?

Before the availability of G-CSF, people with chronic neutropenia had many problems with infection. In some individuals, these infections were life threatening and some died from infection at a young age. Patients who are treated with G-CSF and have a near-normal ANC as a result, should be able to have a normal life expectancy. However, some patients with congenital neutropenia develop life-threatening complications such as MDS or leukemia.

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 that limit quality of life. People differ: the same neutrophil count in different individuals may result in different numbers of infections. The important thing is to reduce the number and seriousness of infections in your child whatever the baseline neutrophil count is.

Is there a safe limit to the amount of time you can take G-CSF?

The SCNIR has information on many individuals who have received long term G-CSF treatment since the late 1980s. It indicates that long term G-CSF therapy is safe and remains effective.

Can you take G-CSF orally?

G-CSF cannot be taken orally because it is a protein that would be destroyed by the stomach and intestines during the digestive process.

Is it safe to have surgery while on G-CSF?

Yes, it is OK to have surgery as long as the surgeon is made 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.

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

Your daughter should be encouraged to participate in all activities with children of her own age. Going away to camp will need special arrangements for storage and administration of G-CSF that can be arranged with the camp doctor/nurse. Alternatively, many pediatric hematology/oncology centers have summer camps in which physicians or nursing staff is able to administer medications.

My son has been receiving G-CSF since he was diagnosed with severe congenital neutropenia three months ago. While he is a lot better he still tends to get breakthrough mouth ulcers, which cause him a lot of discomfort. Is there anything we can do to help alleviate his suffering?

Children may benefit from good mouth care including flossing and regular dental checkups. If the neutrophil count is low, he may also benefit from mouthwashes such as chlorhexidine (Peridex and other brand names) or benzydamine (Difflam). It also may be useful to see your physician to discuss the dose of G-CSF; it may be that the dose needs modifying which could mean an increase.

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 a.) the chances of our child having cyclic neutropenia and b.) any special precautions I should take while pregnant?

The chance of your child also having cyclic neutropenia is 50% as long as your partner does not have cyclic neutropenia as well. This is because cyclic neutropenia is inherited in an autosomal dominant pathway. It would therefore be advisable to see a geneticist to discuss your individual risk.

As G-CSF can cross the placenta to the fetus, it is best to discuss with your physician — before you are pregnant — the G-CSF dosing options and develop a plan to deal with infections that may occur. At this present time, we do not usually recommend the use of G-CSF in the first trimester, if possible. If you are currently pregnant, you should discuss what the dosing should be and what conditions caused by neutropenia would require you to contact your physician (such as fever or an infection).

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 promotion of normal growth and development.

There are no known vitamins, herb supplements or special diets that help raise the neutrophil level.

Can my child participate in school activities?

Yes, providing that your child does not have a significantly enlarged spleen, low platelets or other restricting medical condition, he/she should be able to participate in all sports and other activities in the usual way. The school should be aware of your child's neutropenia and report any injuries to the parent.

What advice should I give to teachers at my child's school?

Explain about your child's diagnosis and ask them to be vigilant for any fever or infections your child may develop. Ensure that they are aware that neutropenia is not contagious and that your child is able to fully participate in all school activities and should be treated differently from any other child. (See below for a letter that can serve as an example).

Where and how can I get in contact with other patients?

Listed below is contact information for patient support groups including websites and phone numbers. Your physician may be able to help you by looking at the SCNIR web page or, contacting the appropriate office in Australia, Germany, the United Kingdom or the USA (see above).

Where can I find more literature on the disease?

The SCNIR web page has a reference list; in addition you can obtain literature by contacting the offices of the Registry (see above).

Information for Schools
Regarding Severe Chronic Neutropenia

To: _____

From: _____

Severe chronic neutropenia (SCN) is the name given to a group of conditions in which neutropenia is the primary problem. The term neutropenia describes the situation where the numbers of neutrophils in the blood is too low. The neutrophils are very important in defending the body against bacterial infections and therefore, a patient with too few neutrophils is more susceptible to bacterial infections. This condition is not contagious and cannot be spread from one person to another. It is a genetic blood disorder.

Neutropenia is treated with injections of a cytokine called G-CSF or "Neupogen". This helps the body create neutrophils to fight infection.

Please help us to fight infections by cleaning minor cuts with an antibacterial soap or Betadine. Please notify me the day of the injury so that I may monitor the wound. For wounds that may need special care please notify me immediately.

For fever above 101°F (38°C) please call me immediately.

If you have concerns about my child's health, you may reach me at the following telephone numbers: _____.

For more information regarding neutropenia, please visit the following websites: SCNIR or the National Neutropenia Network; or contact my child's physician at: _____..

Glossary

ANC (absolute neutrophil count), determined by adding the percentage of neutrophils in the blood with 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 1800-7000.

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.

Alopecia, loss of hair.

Anemia, too few red blood cells.

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 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 deficiency of all types of blood cells, representing a failure of the bone marrow to produce these cells.

Arthralgia, painful joints.

Arthritis, inflammation of joints.

Autosomal dominant, a particular type of genetic inheritance. In a disorder with a dominant inheritance pattern, such as cyclic neutropenia, a child will have the disease if one parent passes on the affected gene. Usually that parent will also have the disorder. 'Autosomal' refers to the fact that the inheritance is independent of the child's sex.

Autosomal recessive, a particular type of genetic inheritance. In a disorder with a recessive inheritance pattern, such as Kostmann syndrome, a child will have the disease only if both parents pass on an affected gene. The parents usually show no sign of the disorder. 'Autosomal' refers to the fact that the inheritance is independent of the child's sex.

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.

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.

Bone marrow transplantation (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 drug treatment to destroy cancer cells.

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.

Cutaneous, concerning the skin.

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

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

Erythrocytes, red blood cells.

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

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 of granulocytes.

G-CSF receptor, a structure on the surface of a cell to which G-CSF binds. Binding of G-CSF to its receptor, provides information to the cell on how to proceed, (e.g., grow, divide, mature, etc.).

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.

Glycogen, a large molecule that serves as a storage form of glucose (sugar).

Granulocyte, a type of leukocyte. The category includes not only neutrophils, but also eosinophils and basophils. However, "granulocyte," "neutrophil," and "polymorphonuclear leukocyte" are often used interchangeably.

Hematopoiesis, the formation of blood.

Hematopoietic growth factor, a protein stimulating the production (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.

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 both copies of the *HAX1* 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.

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.

Neutrophils, a subgroup of granulocytes defending the body against bacteria and fungi. Neutrophils are also known as segs, polys or segmented neutrophils.

Osteopenia, mildly demineralized bone substance.

Osteoporosis, severely demineralized bone substance.

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

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.

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.

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

Vasculitis, inflammation of small blood vessels.

WHIM syndrome, a genetic disorder encompassing **w**arts, **H**ypogammaglobulinemia (low levels of antibody in the blood), **i**nfections, and **m**yelokathexis.

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

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