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 the primary problem is a low number of a type of white blood cell, the neutrophil, which provides defense against bacterial infections. 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 biology, diagnosis, and treatment. We hope that you find it useful in helping you and/or your child in coping with the disease.

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://scnir.org) and the National Neutropenia Network (NNN, http://neutropenianet.org/) or through reading research papers available in our website Bibliography and at Pubmed (https://pubmed.ncbi.nlm.nih.gov/?term=%22severe+chronic+neutropenia%22&sort=date).

The staff and Advisory Board members of the SCNIR wrote this handbook. The SCNIR provides resources for education and research on the causes, consequences, and best treatments for severe chronic neutropenia. The SCNIR was established in 1994 under the sponsorship of Amgen Inc. Since 2000 the U.S. National Institutes of Health (NIH; National Institute of Allergy and Infectious Diseases [NIAID]) has been the principal sponsor of the Registry. In addition to the NIH, it receives support from foundations and private gifts and will greatly appreciate your support if you find its 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 red, blood-forming marrow is located largely within the backbones (vertebrae), breastbone (sternum), and pelvic bones. These bones 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).

The three major types of blood cells:

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

The platelets 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, which also include eosinophils and basophils.

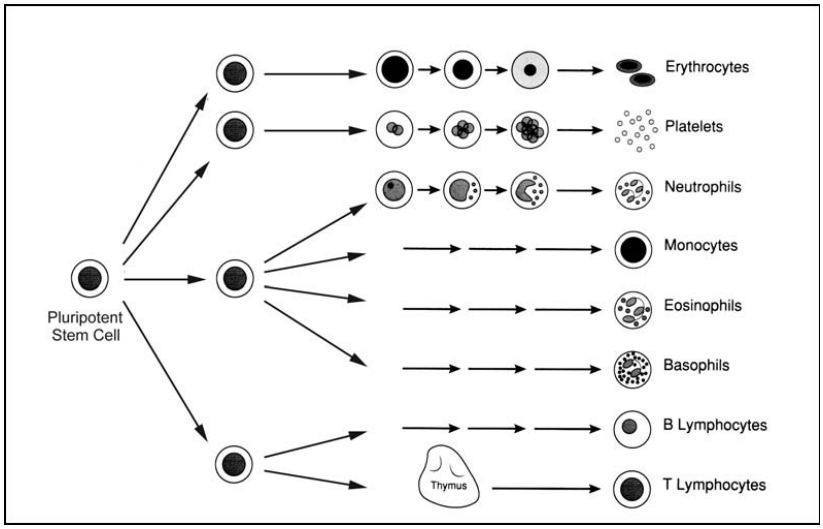


Figure 1. *All types of blood cells are derived from one single 'mother cell', the pluripotent hematopoietic stem cell. "Pluripotent" means the cell can produce all different types of blood cells.*

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 bloodstream 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. 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 three months after they leave the bone marrow, whereas platelets live for just a few days and neutrophils circulate in the blood for only a few hours (although that remains controversial).

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, and often neutropenia occurs after a viral infection. Some people are born with neutropenia (congenital neutropenia), and in many cases the reasons are not known (idiopathic neutropenia).

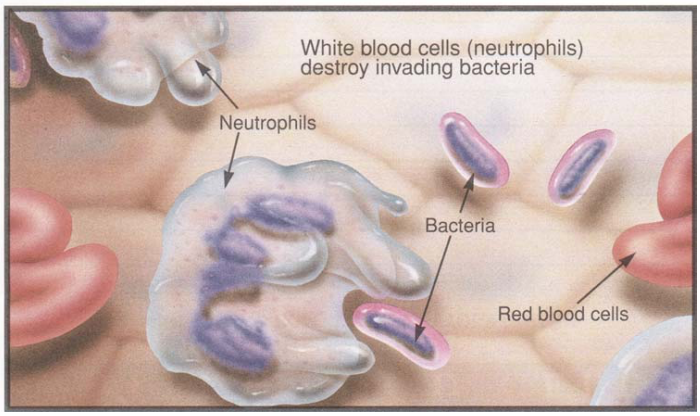
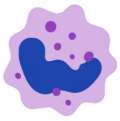


Figure 2. *An artist's view of neutrophils attacking bacteria in the bloodstream.*

The level of neutropenia may vary considerably. In general, the blood of healthy adults contains about 1500 to 7000 neutrophils per cubic millimeter (mm^3). 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 – see link for how to calculate) and is described as:



Mild neutropenia: ANC below 1500 per mm^3, but above 1000 per mm^3. (Many laboratories express these numbers in thousands, so ANC 1500 would be 1.5 x thousand per mm^3.)

Moderate neutropenia: ANC between 500 and 1000 per mm^3.

Severe neutropenia: ANC below 500 per mm^3.

Very severe neutropenia (sometimes termed "agranulocytosis"): ANC below 200 per mm^3.

The duration of the neutropenia may be short, in which case, the patient is described as having transient 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 both the level and duration 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 (ear infections); tonsillitis; sore throat; mouth ulcers; gum infection and skin abscesses. Serious infections include pneumonia, peritonitis (inflammation in the abdomen), and sepsis (bloodstream infection).

The risk of infection also depends on whether the neutropenia is due to lack of production of neutrophils (e.g. congenital neutropenia) or to destruction of normally produced neutrophils (e.g. autoimmune neutropenia).

Severe neutropenia can lead to serious problems, which require prompt care and attention as the patient could potentially develop a bacterial infection at any time. These infections can be life threatening when a patient has persistent severe neutropenia. Any fever (body temperature above 38.5°C/101.3°F) must be taken very seriously and the patient's medical provider should be informed. It is important that the patient sees a medical provider as soon as possible and is treated with medications (such as antibiotics) to fight the infection.

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 section gives examples of some of the different types of chronic neutropenias.

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 4) 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.

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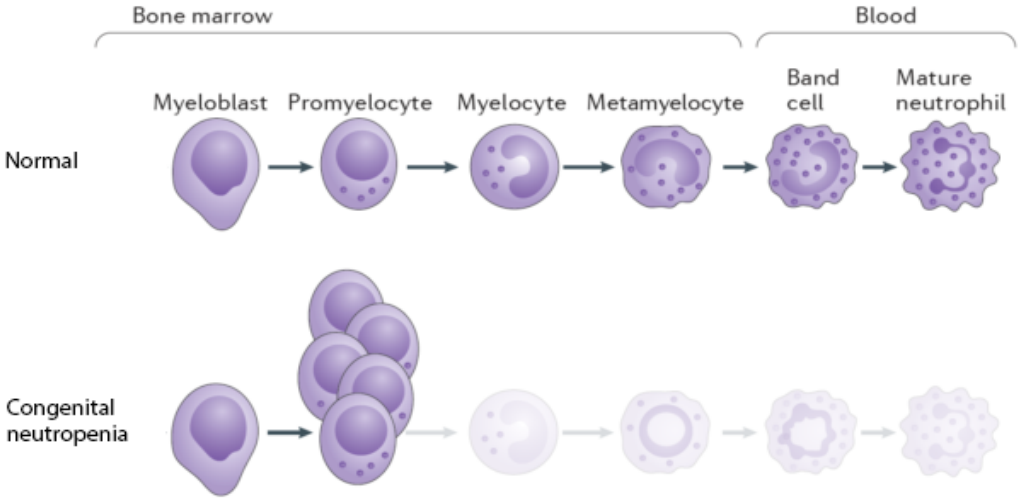


Figure 4. *In healthy individuals, the maturation of granulocytes leads to segmented neutrophils, which leave the bone marrow and enter the blood. In congenital neutropenia patients, the maturation pathway is blocked at the stage of early precursor cells, the promyelocytes.*

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

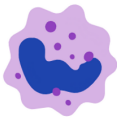
Cyclic neutropenia is another inherited type of neutropenia. As the name indicates, in this disease neutrophil counts show a cyclic pattern with a typical cycle length of 21 days. These cycles vary from patient to patient. Some individuals remain neutropenic during the whole cycle with regular periodic further declines in the neutrophil count, while others have low neutrophil counts for only a few days and normal blood counts during the rest of the cycle. Those who have a longer neutropenic period within the cycle suffer more frequently from infections compared with patients who have only short neutropenic phases. Monocytes often rise when the neutrophil counts drop.

Almost all patients with cyclic neutropenia have periods of severe neutropenia (ANC less than 200 per mm^3) every three weeks with some symptoms almost every cycle, such as fever, fatigue, and mouth sores. Significant infections (e.g., pneumonia or bloodstream infection) are infrequent but may be severe and life-threatening. 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.

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.

Shwachman-Diamond Syndrome

Shwachman-Diamond syndrome (SDS) is an inherited (autosomal recessive) condition with multisystem abnormalities including pancreatic insufficiency (problems with digestion of fats in the diet), neutropenia, and short stature (height). At the time of diagnosis, the features of SDS are extremely variable. Many



patients are diagnosed in infancy, with symptoms of fatty stools/diarrhea and poor growth, with or without neutropenia. Other less common features can also be present at diagnosis. These include short stature, skeletal abnormalities, and, in infancy/early childhood some patients develop marked liver enlargement with elevated liver enzymes which improve spontaneously over time. 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, so 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 (low red blood cells) and/or thrombocytopenia (low platelet count).

Similar to congenital neutropenia, patients with SDS have an increased risk of 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 glucose (sugar) metabolism. The liver, spleen and other tissues accumulate *glycogen*. In addition to neutropenia and decreased neutrophil function, patients often have enlarged liver and spleen, intestinal problems (inflammatory bowel disease), poor growth, kidney problems, hypoglycemia (low blood sugar) and recurrent infections. The presence of an enlarged spleen can be associated with low red blood cells (anemia) and thrombocytopenia, whereas neutropenia is always present. Patients respond to treatment with G-CSF as well as to a new treatment with oral empagliflozin, a repurposed anti-diabetes drug.

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.

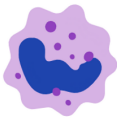
Idiopathic Neutropenia

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. 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 other causes.

Autoimmune Neutropenia

In neutropenic children aged 6 months to 4 years the presence of neutrophil-specific *antibodies* can result in increased destruction of neutrophils by the child's own immune system. 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 develop 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 followed closely by their medical team 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 provider. For the few children who develop severe infections or have significant impairment of lifestyle (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 primary SCN described. The main conditions that may include neutropenia are:

Viral illnesses – the most common cause of transient neutropenia
Acquired aplastic anemia
Chemotherapy or radiotherapy
Other drugs
Bone marrow failure syndromes that affect multiple blood cell types

There are some other very rare disorders, congenital or acquired, that may be associated with neutropenia, as well as hereditary disorders of immune regulation (e.g. hyper IgM syndrome, severe combined immunodeficiency, autoimmune lymphoproliferative syndrome, and many others).

Genetics of Severe Congenital Neutropenia

Recent research, including many studies 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 most forms of severe congenital neutropenia. Severe congenital neutropenia can occur in a sporadic pattern, in an autosomal dominant fashion, or as an autosomal recessive disorder. Mutations in the *ELANE* gene (formerly termed *ELA2*) are responsible for 60% of severe congenital neutropenia cases. Additionally, rare cases of autosomal dominant severe congenital neutropenia can arise from mutations in other genes. The autosomal recessive form of severe congenital neutropenia associated with mutations in the *HAX1* gene is sometimes called Kostmann syndrome. 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 remote chance of being passed on to the next generation. Genetic counseling is very helpful for families to understand risks for relatives and future children.

Much rarer causes of neutropenia include syndromes affecting other cells or organs or interfering with immune function. In Shwachman-Diamond syndrome 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 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. *WHIM* syndrome is transmitted as an autosomal dominant disorder.

Diagnostic Tests Used in Severe Chronic Neutropenia

When a diagnosis of neutropenia is suspected providers will begin by taking a Complete Blood Count (CBC) with differential ("CBC/diff") and proceed to further tests if necessary. 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. By this procedure the neutrophil count is measured. If the neutrophil count is low, it is normal to repeat the CBC to be certain that the neutropenia continues. In patients with severe congenital neutropenia the neutrophil count may vary slightly, but it always remains at a very low level in contrast to cyclic neutropenia, where it varies regularly.

Other Blood Tests

Other blood tests may be performed to test for causes of secondary neutropenia, e.g. infections, rheumatologic conditions, immunological disorders.

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.

Bone marrow cells are usually taken from the large pelvic bone, the ilium. This is usually done with local anesthetic and sedation, but sometimes under anesthesia. The actual technique may vary between treating centers. Your provider will explain exactly how the procedure will be done for you. Here is one example, with good illustrations but some aspects (e.g. NHS letter) and drug names specific to Great Britain: (https://www.youtube.com/watch?v=tI7m2y_secI).

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 sample of bone marrow is taken using a hollow needle to look at the architecture of the marrow structure.

When a bone marrow sample is taken for diagnostic purposes, the cells are examined under the microscope and often are used for other investigations, such as cytogenetics (see below). If possible, and with informed consent, a sample is sent to the SCNIR bone marrow cell bank to be used for research.

In congenital neutropenia, the bone marrow usually (but not always) shows a "maturation arrest" in which the precursor cells that should develop into neutrophils fail to mature fully. In acquired neutropenia, such as autoimmune or idiopathic, the bone marrow usually shows full neutrophil development.

For some forms of acquired neutropenia the diagnosis can be established without a bone marrow examination.

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. 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 for congenital neutropenia.

There are additional techniques, such as fluorescence in situ hybridization (FISH) by which some chromosomal and other genetic changes (e.g. somatic mutations) can be monitored; your provider will explain these to you.

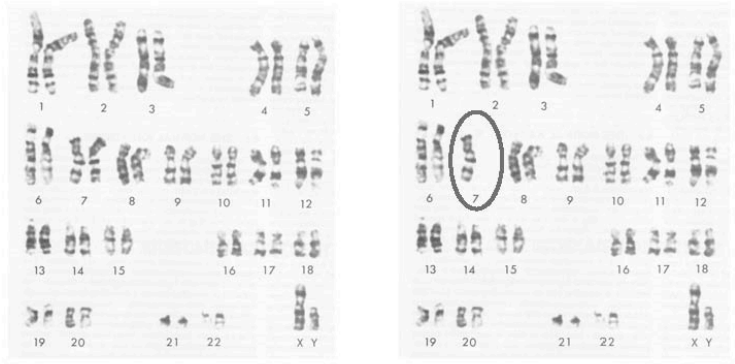


Figure 4. *Each human cell (except for eggs and sperms) contains 23 pairs of chromosomes. Pre-leukemic changes may be represented e.g. by the loss of one copy of chromosome 7 as shown on the right panel.*

Other Investigations

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) additional tests may be necessary. Your provider will explain what further tests are required. Sometimes this may involve visits with other specialists.

Treatment for Severe Chronic Neutropenia

Treatments prescribed by your provider are extremely important to decrease the potential for infection. Good nutrition and hygiene (including good dental hygiene) are also very important. Although a healthy diet is good for everyone, nutritional treatments will not raise the neutrophil count in severe chronic neutropenia. Patients should discuss specific treatment options with their provider. These discussions should include the benefits of treatment and potential risks.

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

If congenital neutropenia is diagnosed, most patients begin treatment with a growth factor called granulocyte colony-stimulating factor (G-CSF). This treatment stimulates an increase in the neutrophil count, leading to improved life expectancy and quality of life. 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.

G-CSF is a natural cytokine produced by the human body. A cytokine is a protein produced by cells for the regulation of other cells. Patients with congenital neutropenia also produce G-CSF, but not in

amounts adequate to correct the severe neutropenia. It is also effective for many forms of acquired neutropenia, although in such cases it is not always necessary.

The response to G-CSF treatment varies among neutropenia patients, even among those with the same diagnosis. 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/day may be evaluated for possible hematopoietic stem cell transplantation (discussed below).

G-CSF is usually administered by a subcutaneous injection (injection just under the skin). Recommended sites include the abdomen below the navel (belly button), upper outer arms, and upper outer thighs (see instructions). 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. Rotation of the sites is recommended to prevent scarring and discomfort. The injection is usually not painful, but occasionally a stinging sensation may be experienced for a short period of time on administration.

Treatment with G-CSF usually produces a dramatic increase in the numbers of neutrophils in the blood and is the most effective therapy in treating SCN. Some SCN patients receiving G-CSF report bone or muscle pain, injection site reactions, and spleen enlargement (usually mild). Other very infrequent side effects include decreased platelet count, rash, enlarged liver, joint pain, osteoporosis (see below), and exacerbation of some pre-existing skin disorders (e.g., psoriasis). If these or other side effects occur, notify your health care provider. In addition, cytogenetic abnormalities, transformation to *myelodysplastic syndrome* and *leukemia* have been observed in patients with congenital neutropenia treated with G-CSF (this issue is discussed in detail below).

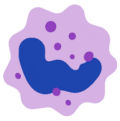
Hematopoietic Stem Cell Transplant

Hematopoietic stem cell transplant (HSCT) is the only curative treatment for severe congenital neutropenia. It may be considered for failure to respond to G-CSF treatment, or for patients who develop MDS or leukemia, or whose bone marrow examinations show early signs of progress to MDS. Due to the higher risk of MDS and leukemia in SCN with a poor response to high doses of G-CSF (see above), some individuals in this group may also be considered for HSCT. Transplantation is an intensive procedure, carrying serious risks, and is therefore not recommended as a first-choice treatment. It is important for the patient and provider to discuss in detail potential risks and benefits.

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. 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 stem cells from bone marrow (multiple needle punctures, under anesthesia) or blood (collected from one vein, processed through a cell separator, and returned to another vein by a process called *pheresis* or *apheresis*). 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.

Other Treatments

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 a very 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.



Gene therapy:
Current research by SCNIR and other investigators is exploring several different approaches to correcting the genetic defects that cause severe congenital neutropenia. If successful, such therapy could permanently cure the disease, but the research has not yet reached the stage of clinical trials. The SCNIR will communicate when clinical trials are available.

New agents:
One oral drug, Mavorixafor, is currently in clinical trials for *WHIM syndrome* and some other forms of neutropenia. Other potential drug treatments are being explored in basic research laboratories but are not yet being considered for clinical trials.

Corticosteroids:
Steroids are NOT recommended for treatment of chronic neutropenia. These drugs release neutrophils from the bone marrow to enter the blood stream. However, they do not induce the production of new neutrophils in the bone marrow, and they decrease the function of neutrophils and other types of white cells, thus actually 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., weak bones (osteoporosis), diabetes, cataracts).

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 (e.g. brushing and flossing) is very important and the use of an antibacterial mouthwash may be recommended.

Immunizations and vaccinations: People with SCN have an intact immune system that allows them to respond normally to vaccines. 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. Washing of household, playground, or work items is not necessary.

Prophylactic (preventive) antibiotic or antifungal medication may be given to neutropenia patients, but this is very much based on individual provider choice but is NOT a standard part of treatment. Chronic use of antibiotics can promote the emergence of antibiotic-resistant bacteria.

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

Foreign travel: Concerns should be raised with your provider, 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 https://severe-chronic-neutropenia.org/de/partner

Diet: 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, herbal supplements or special diets that help raise the neutrophil level. The so-

called “neutropenic diet” provides no protection from infection and may be less nutritious than a standard, well-balanced diet.

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 activities. These includes school or work, 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 evaluation gives the provider the information needed to monitor your ANC. Monitoring the ANC alerts the provider 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 CBC every 3 months. 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 drawn just prior to the next administration of the medication. This allows the provider to monitor the ANC at its lowest point.

Bone Marrow Monitoring

Bone marrow aspirate and biopsy procedures are done initially to help the provider 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 examinations (including cytogenetic and molecular evaluations) to monitor for changes in their bone marrow. Early detection of changes indicating progression towards MDS or leukemia through bone marrow monitoring can lead to more successful therapy.

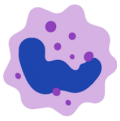
SCN patients with types of neutropenia other than congenital neutropenia (such as cyclic, idiopathic, or autoimmune) may have bone marrow testing at the discretion of their provider.

Pregnancy

Data on the use of G-CSF during pregnancy are limited, but in all publications, the use of G-CSF throughout pregnancy has been documented to be safe and well tolerated. Available data support the continuation of G-CSF treatment in women with different types of SCN throughout the pregnancy to prevent major infections and newborn complications. The recommendation is based on the high risk for bacterial infections and septic death in untreated severe congenital neutropenia. The Registry recommends G-CSF treatment for all patients with ANC below 500 per mm^3 if they were on G-CSF treatment before pregnancy. For those who are not already on treatment, G-CSF treatment should also be considered.

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 and wish 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 child with SCN 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.

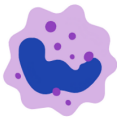
All school-aged children utilize school for socialization and academic development. This development is essential to help the child move through the milestones of childhood. The SCN child will need all caregivers (such as schoolteachers, school nurses, day-care providers, coaches, etc.) to understand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

Adolescence is a difficult time for anyone, and those with SCN realize, often for the first time, that they are different from their peers. This may be the first time the young person 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.

Risk of Myelodysplastic Syndrome and Leukemia

Data from the SCNIR and other registries have shown that patients who have severe congenital neutropenia (but not acquired neutropenia) have an increased risk of developing myelodysplastic syndrome (MDS) or leukemia compared with healthy individuals. The risk of MDS or leukemia is not completely understood but current estimates for severe congenital neutropenia are around 20% after 15 years on treatment with G-CSF. 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 just correlates with disease severity or if there is a potential effect of G-CSF to promote the development of leukemia – both are possible. In the era before G-CSF, some of the few 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) without G-CSF treatment. For most patients, the risk of infection without G-CSF treatment outweighs



the risk of eventual [potential?] leukemia. In addition, hematopoietic stem cell transplantation, the alternative to G-CSF treatment, has significant risk.

Importantly, patients with acquired (e.g. idiopathic or autoimmune) neutropenia do NOT appear to be at risk for MDS or acute myeloid leukemia (AML), whether or not they receive G-CSF therapy. Patients with cyclic neutropenia also have a very much lower risk than those with other forms of severe congenital neutropenia.

The SCNIR recommends that all patients with all types of severe congenital neutropenia, except cyclic neutropenia, have a bone marrow examination on a yearly basis. A bone marrow examination is also recommended any time there is an apparent failure of G-CSF treatment or an unexplained change in blood counts, such as lower numbers of platelets or red cells, or loss of response to G-CSF. Transplantation should be considered if the bone marrow or chromosome pattern shows abnormalities indicating potential conversion to MDS or leukemia.

Bone marrow examinations should include morphology (analysis of cell number, size, and shape by an experienced pathologist), cytogenetics (chromosome analysis), and molecular testing for acquired mutations in genes related to myelodysplasia and leukemia.

Risk of Osteopenia/Osteoporosis

Patients with chronic neutropenia on G-CSF therapy have an increased risk of 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 *DEXA scan* followed by referral to an endocrinologist if the DEXA scan is abnormal. DEXA scans in children require reference ranges different from adults and should be interpreted by a pediatric endocrinologist with expertise in bone density.

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 providers who treat them by providing the most up-to-date information on the natural history of SCN and its treatment options.

The objectives of the SCNIR are to:

> Understand 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 adverse events such as osteoporosis, splenomegaly, thrombocytopenia, cytogenetic abnormalities, myelodysplastic syndrome (MDS), and leukemia.
>
> Establish a provider 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 the time of medically necessary bone marrow examinations for current and future research.

The SCNIR Advisory Board of expert physicians and scientists helps to guide the Registry in its support of research investigators, patients, and families.

A panel of European physicians/hematologists called the Local Liaison Physicians located throughout the European countries can be found on the web site https://severe-chronic-neutropenia.org/en/partners

Patients qualify for the Registry if:

Multiple ANCs are under 500 per mm^3, preferably on at least three occasions in the three months prior to registration for the Registry (if currently treated, three ANCs under 500 per mm^3 prior to the start of G-CSF therapy) with the exception of patients with Shwachman-Diamond syndrome, glycogen-storage disease type 1b and Barth syndrome who are enrolled with higher ANCs or even no neutropenia at all.
Or, there is a genetic diagnosis of congenital neutropenia.

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 unrelated to congenital neutropenia
- Leukemia unrelated to congenital neutropenia
- Aplastic anemia
- Known immune or rheumatologic diseases such as lupus
- The patient has had chemotherapy for cancer within the past 5 years.

Patients qualifying for the Registry will be offered an informed consent document to sign if they wish to enroll.

In the USA

Severe Chronic Neutropenia International Registry
Boston Children's Hospital
Email: SCNIR-dl@childrens.harvard.edu
Phone: 617-919-1574
Fax: 617-730-4679
SCNIR.org

University of Washington (Seattle) office
Email: bolyard@uw.edu
Phone: 206-543-7218

In Europe

Severe Chronic Neutropenia International Registry
Phone: +49 (511) 557105
FAX: +49 (511) 557106
severe-chronic-neutropenia.org/en

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
Phone: 1-866-600-0799
Email: jeanne@neutropenianet.org

Schwachman-Diamond Syndrome Foundation
Phone: 1-888-825-SDSF (7373)
Email: info@shwachman-diamond.org

Barth Foundation
Phone: 855-662-2784 or 855-NO-BARTH

Canada

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

Europe

Neutropenia Interest Group
Phone: +49 016 39151834
Email: klaus.schmid@neutropenie-ev.de

Frequently Asked Questions and Answers

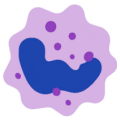
Will my child with chronic neutropenia develop normally, especially in their growth and development?

Children with chronic neutropenia 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 for some vaccinations, is that safe?

In general, it is safe for children and adults to have vaccinations, including live virus vaccines (e.g. chicken pox/varicella) and influenza and COVID immunizations. Neutropenia is not a contraindication to vaccinations. All routine vaccinations are recommended to be given at the standard ages and time intervals. However, if your child also has an additional non-neutropenia immunodeficiency, they may need to avoid live vaccines so this should be discussed with your doctor.

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 white blood 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 and abrasions 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. 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 discuss it with your provider.

When should my child start G-CSF?

Your child should start G-CSF therapy if they are 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. Some families choose to start G-CSF to improve quality of life, e.g. to avoid frequent emergency room visits.

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.

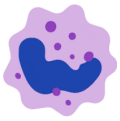
Is it safe to have surgery while on G-CSF?

Yes, it is safe, and generally preferable, to continue G-CSF therapy when you 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 child wants to attend a camp with her school. 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. What is your 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 provider to discuss the dose of G-CSF; it may be that the dose needs to be modified/increased.

I have cyclic neutropenia and inject G-CSF three times a week. My partner and I are getting married in a few months and would like to start trying for a family. Can you give me any advice on the chances of our child having cyclic neutropenia and 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 pattern. It would therefore be advisable to see a geneticist to discuss your individual risk. Please see the section on pregnancy, above.

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, they should be able to participate in all sports and other activities in the usual way.

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. Ensure that they are aware that neutropenia is not contagious and that your child is able to fully participate in all school activities; they 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 above is contact information for patient support groups including websites and phone numbers.

Where can I find more literature on the disease?

The SCNIR web page reference list includes a frequently updated set of medical literature references. As for issue medical issues, do not believe everything you find on the internet – many sources are unreliable or alarmist.

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.

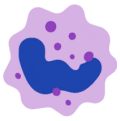
Neutropenia may be treated with injections of a medication called G-CSF or filgrastim, as well as "bioequivalents." These medications help the body create neutrophils to fight infection. Current brand names include Neupogen, Nivestym, Granix, Zarxio, and Releuko

Please help us to fight infections by cleaning minor cuts with an antibacterial soap or antiseptic. 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 provider 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 number 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.

Apheresis (see Pheresis, below)

Aplastic anemia, a deficiency of all types of blood cells, due to 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, 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.

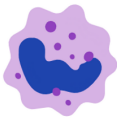
Basophils, a subgroup of granulocytes, normally very low in number.

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 cell types present in the blood.

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.

Clinical trials, research studies that test a medical, surgical, or behavioral intervention in people. These trials are the primary way that researchers determine if a new form of treatment is safe and effective.

Cutaneous, concerning the skin.

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

Cytokines, signaling proteins made by blood cells to stimulate or otherwise affect the production or function of other blood cells.

DEXA scan, a bone density scan that uses low-dose x-rays to measure calcium and other minerals in your bones.

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

Erythrocytes, red blood cells.

Filgrastim, the international non-proprietary name for recombinant human G-CSF.

Fluorescence in situ hybridization (FISH), a microscopic technique for visualizing normal and abnormal chromosomes or rearranged genes within cells.

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).

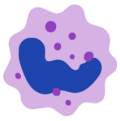
Granulocyte, a type of leukocyte. The category includes not only neutrophils, but also eosinophils and basophils. However, "granulocyte," "neutrophil," and "polymorphonuclear leukocyte" are often used interchangeably.

Hematopoiesis, the formation of blood.

Hematopoietic growth factor, a protein stimulating the production 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 may be 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 weak (demineralized) bones.

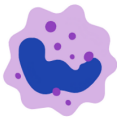
Osteoporosis, severely weak (demineralized) bones.

Pheresis, a procedure in which blood is continuously withdrawn and separated into its components; one or more components (e.g. stem cells, red cells) are retained and the rest are returned to the donor by continuous transfusion.

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.

Provider, a physician, nurse practitioner, physician assistant, or other health care provider.

Psoriasis, a disease characterized by scaly skin**.**

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

Somatic mutation, a change (e.g. mutation) in a person's DNA that occurs after conception to any cell that isn't a germ cell (egg or sperm cell)

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

X-linked recessive, an inheritance pattern due to a gene on the X chromosome. In this pattern, there is a 50% chance of the same disease in a mother's other sons. 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.