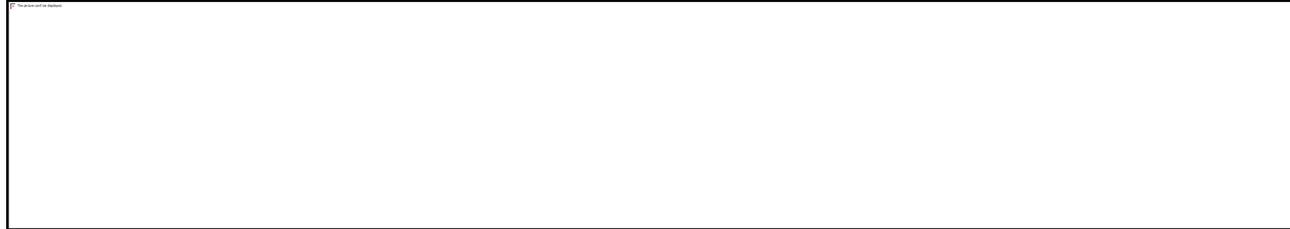


# Neutropenia Management



# Introduction:



Neutrophils or leukocytes develop from the stem cells in the blood marrow.

These cells are polymorphonuclear involved in acute inflammation and host defense against bacterial infections and phagocytosis occurs in these cells.

# Introduction:

1–1.5×10<sup>9</sup>/kg neutrophils are produced daily in the human body and they are found in the storage pool in the bone marrow. Only 2–5% enter the circulation. A portion of these cells are located on the vascular wall

# Introduction:

The average lifespan of neutrophils is 7–10 days. Maturation stages in the bone marrow are as follows: stem cell, myeloblast, promyelocyte, myelocyte, metamyelocyte, band and neutrophil. The cells do not divide after the stage of myelocyte. Generally, half of the cells in the bone marrow are composed of white blood cells. there for 2–3 days

# Introduction:

The majority of these cells include metamyelocytes and the following mature cells. The band cells and neutrophils in the bone marrow constitute 50% of the granulocyte series. Mature neutrophils are transferred to the tissues after staying in the circulation for 3–12 hours and live there for 2–3 days

# Introduction:

For neutrophils to function adequately, they should primarily be produced in adequate numbers in the bone marrow, should be transferred to the peripheral circulation in adequate numbers, migrate rapidly to the area of infection and engulf and kill microorganisms. One of the most important one among these necessary features is adequate number of neutrophils

# Introduction:

An absolute neutrophil count (ANC) below the normal level by age and race is defined as neutropenia.

# Introduction:

The lower limit of neutropenia in newborns is  $6000/\text{mm}^3$ . As the baby grows up, this limit reduces to  $1\ 000/\text{mm}^3$  by the second week and this level is accepted to be normal up to the age of one year. After the age of one year the lower limit is  $1\ 500/\text{mm}^3$ . In the black race, this limit is accepted to be  $1200/\text{mm}^3$

# Introduction:

The absolute/total neutrophil count=  
WBC count X (PMN percentage + Band  
cell Percentage)/100

# Introduction:

Neutropenias are classified by absolute neutrophil count as follows:

1 000–1 500/mm<sup>3</sup>: mild neutropenia

500 – 1 000/mm<sup>3</sup>: moderate neutropenia

<500/mm<sup>3</sup>: severe neutropenia

<100/mm<sup>3</sup>: very severe neutropenia

# Introduction:

Predisposition to infection is increased in neutropenia. This relation has been known well since 1960s.

# Introduction:

However, the main determinant in the relation of neutropenia and infection is not always the neutrophil count. In clinical practice, there are patients who have never had infection or severe infection, though their neutrophil counts are below  $500/\text{mm}^3$ . In this case, the determinant is not the count of circulating neutrophils, but the neutrophil storage in the bone marrow..

# Introduction:

If the storage is enough, no infection occurs. The severity of neutropenia and the frequency and severity of infection are inversely proportional.

# Introduction:

If cell production in the myeloid series is decreased or the storage is reduced in the bone marrow, the risk of infection is high. In neutropenia caused by increased destruction in the peripheral blood, the risk of infection is lower.

# Introduction:

If neutropenia is not alone and is accompanied by neutrophil dysfunction, hypogammaglobulinemia or malnutrition and the patient's age is young, the risk of infection increases further

# Introduction:

The agent in neutropenic patients is usually the endogenous flora. The gingiva, nail beds and anal region should be examined carefully in all neutropenic patients.

# Introduction:

The signs of infection may be suppressed in these patients, but fever is almost always observed as a finding of inflammation.

If a neutropenic patient has no fever, though he/she looks ill, the picture is very severe and the patient is usually lost in a short time.

# Introduction:

In the period of neutropenia, the neutrophil count is attempted to be increased by using growth factors. Granulocyte colony stimulating factor (G-CSF) is one of these growth factors which enables maturation of the neutrophil precursors by stimulating them and lets them be transferred to the peripheral blood earlier

# Causes of neutropenia

- 1) Decreased production
- 2) Inability to be transferred from the bone marrow to the peripheral blood (ineffective production)
- 3) Increased margination-sequestration (pseudoneutropenia)
- 4) Increased destruction

# Causes of neutropenia

Neutropenia may also be classified as

1)acute or chronic

2)acquired or congenital.

# Causes of neutropenia

If a finding persists longer than 14 days, it is generally considered to have become chronic in medicine. For neutropenia this period is stated to be two months in some books and six months in some others. It has been stated that correction of neutropenia even following a simple event may last for up to 8–12 months.

# Causes of neutropenia

Therefore, it is thought that calling neutropenia “chronic” before 6 months is not very appropriate

# Causes of neutropenia

There are two more neutropenia types with unclear etiology which are difficult to classify as acquired or congenital and which are observed in the childhood: **chronic benign neutropenia** and **familial neutropenia**.

# Chronic benign neutropenia

Chronic benign neutropenia is the most common cause of neutropenia in children **below the age of four years** in cases where an **infection cannot be demonstrated**. There is **no underlying infectious, inflammatory or malign disease** in these patients. There is no history of similar disease in the **family**.

# Chronic benign neutropenia

The absolute neutrophil count ranges between 200 and 500/mm<sup>3</sup>. The disease has a benign course independent of the severity of neutropenia. In these patients, the bone marrow is either normal or an increase in the myeloid precursors is observed and maturation is observed to be paused in the late stage. Rarely, anti-neutrophil antibodies are found in the sera of the patients.

# Chronic benign neutropenia

However, the etiology is still not clear. In the beginning, corticosteroids, splenectomy and cytotoxic agents were being used in treatment targeting the antibodies, but adequate response could not be obtained. Currently, the risk of infection is successfully reduced with G-CSF. However, G-CSF is recommended to be used in cases of repetitive infection complications because of the benign character of the disease

# Benign familial neutropenia

Neutropenia is observed more commonly in some ethnic groups. Neutropenia is mild and therefore, there is no predisposition to infections. It has an autosomal dominant inheritance and examination of the bone marrow is normal. Therefore, blood counts of the parents and siblings should also be examined even if there are no complaints in neutropenic patients

# Acquired neutropenias

The cause of neutropenia in acquired neutropenias is shortening of the neutrophil lifespan because of destruction or increased consumption of the neutrophils in the peripheral blood. The bone marrow is normal or there is pausing in late maturation in the metamyelocyte/band stage. The risk of development of infection in acquired neutropenias is substantially lower compared to the other neutropenias

# Acquired neutropenia

## 1. Infection-related neutropenia

- Since infections are observed commonly in children, the most common cause of neutropenias observed in this period is also infections. Acute transient neutropenias most commonly occur after viral infections. Acute transient neutropenia starts in a few days before the onset of infection and continues until viremia ends.

# Acquired neutropenia

## 1. Infection-related neutropenia

- Viral infections including varicella, measles, rubella, hepatitis A and B, influenza, cytomegalovirus, Epstein-Barr virus, parvovirus B19, adenovirus and coxsackie lead to neutropenia by causing to a reduction in production and increase in destruction. In “human immunodeficiency virus infection”, immune mechanisms in which anti-neutrophil antibodies and hypersplenism are involved are also effective.

# Acquired neutropenia

## 1. Infection-related neutropenia

- Neutropenia may also be observed in bacterial infections including *S. aureus*, brucella, rickettsia and tuberculosis.
- Use of G-CSF may be beneficial in patients with neutropenia caused by depletion of storage pools in the bone marrow and inadequate production in severe sepsis

# Acquired neutropenias

## 2. Neutropenia related with medications

Currently, many different medications may lead to neutropenia. Dose-dependent bone marrow suppression is observed most commonly with chemotherapy drugs, phenothiazines, semi-synthetic penicillins, non-steroid anti-inflammatory drugs, aminopyrine derivatives, barbiturates, gold compounds, sulfonamides and antithyroid drugs.

# Acquired neutropenias

## 2. Neutropenia related with medications

Neutropenia develops in 2–3 months with use of medications and it is expected to improve in approximately 10 days with discontinuation of the drug, but this period may sometimes be longer.

# Acquired neutropenias

## 2. Neutropenia related with medications

Rarely, neutropenia may occur as a result of idiosyncratic suppression of myeloid production with antibiotics, anti-diabetics, antihistaminics and antihypertensive drugs, destruction of neutrophils related with differences in drug metabolism (phenothiazine, thiouracil) and leukocyte destruction due to antibodies developing against the leukocyte-drug complex (phenylbutasone, chlorpropamide)

# Acquired neutropenias

## 3. Autoimmune neutropenia

This is a chronic neutropenia which occurs because of destruction of neutrophils by neutrophil specific IgM and IgG antibodies produced against NA1, NA2, ND1, ND2 and NB1 antigens in neutrophils. Autoimmune neutropenias may be related with secondary causes or may occur primarily without being related with any disease

# Acquired neutropenias

## 3. Autoimmune neutropenia

a) Primary autoimmune neutropenia This occurs rarely and is observed mostly in girls and in children below the age of two years. Recurrent mild cutaneous and upper respiratory tract infections are found commonly. The gold standard in the diagnosis is demonstration of neutrophil specific autoantibodies, but negative autoantibodies do not exclude the diagnosis. The bone marrow is normal.

# Acquired neutropenias

## 3. Autoimmune neutropenia

### a) Primary autoimmune neutropenia

The disease has a good prognosis and neutropenia generally improves spontaneously. The total neutrophil count ranges between 0 and  $150/\text{mm}^3$ , but infections are mild. Most patients are given prophylactic antibiotic (trimethoprim-sulfa-methoxazole), whereas immunosuppressive drugs are not used. If there is a severe infection, high dose intravenous immunoglobulin and G-CSF may be used in addition to antibiotics.

# Acquired neutropenia

## b) Secondary autoimmune neutropenia

This is usually observed in adults. It constitutes a part of autoimmune diseases.

It occurs less commonly compared to autoimmune anemia and thrombocytopenia.

Cytotoxic drugs including cyclosporin and methotrexate directed to antibody are used in treatment.

G-CSF may be used to reduce the risk of development of infection especially when the neutrophil count reduces below  $1000/\text{mm}^3$ . the cause of the disease

# Acquired neutropenia

## b) Secondary autoimmune neutropenia

When secondary autoimmune neutropenia is considered in children, autoimmune lymphoproliferative syndrome (ALPS) and Evans syndrome should be considered primarily, if rheumatic disease is not considered. Both diseases are characterized with lymphadenopathy, splenomegaly and autoimmunity.

# Acquired neutropenia

## b) Secondary autoimmune neutropenia

When autoimmune neutropenia is associated with hemolytic anemia and thrombocytopenia, Evans syndrome should be considered.

Increased apoptosis as a result of Fas mutations is the cause of the disease

# Acquired neutropenias

- 4. Isoimmune neonatal neutropenia
- This is similar to Rh hemolytic disease of the newborn. It occurs as a result of destruction of neutrophils by way of placental transfer of the antibodies produced in the sensitized mother against HNA1, HNA2, HNA3, HNB1 and HNC1 antigens in the baby's neutrophils.
- In brief, it may be described as Rh disease which occurs against neutrophils rather than red blood cells.

# Acquired neutropenias

- 4. Isoimmune neonatal neutropenia
- The disease which is characterized with moderate of severe neutropenia occurs in 2 of 1000 live births.

# Acquired neutropenias

- 4. Isoimmune neonatal neutropenia
- Although it does not generally cause too many problems, bone marrow examination should be performed in neutropenic newborns who have severe infections including recurrent bacterial infection or sepsis and granulocyte transfusion or G-CSF should be administered, if pause in early maturation is found

# Acquired neutropenias

## 5) Hypertensive Mothers

Neutropenia starting immediately after delivery and lasting for up to 30 days may occur in approximately 50% of the babies of hypertensive mothers. Thrombocytopenia frequently accompanies neutropenia. Bone marrow suppression is found in these babies

# Acquired neutropenias

6) in burns and ARDS

In addition, complement is activated, margination of neutrophils increases and pseudoneutropenia may occur in burns and acute respiratory distress syndrome.

# Acquired neutropenias

Similarly, neutropenia may develop with neutrophil destruction as a result of activation of complement in paroxysmal nocturnal hemoglobinuria. In folic acid, copper and vitamin B12 deficiency, neutropenia may occur because of ineffective myelopoiesis in addition to megaloblastic anemia

# Neutropenias due to hereditary causes

These neutropenias develop in relation with disruption in any stage of growth or maturation of neutrophils. They occur rarely, but are important because they lead to recurrent infections and have a chronic course.

# Neutropenias due to hereditary causes

After 2000s, congenital severe neutropenias have been started to be resolved genetically. Early apoptosis is the cause of neutropenia in most of these neutropenias

# 1. Kostmann syndrome

Kostmann syndrome was described by Swedish Kostmann for the first time in 1956. The most important finding of the disease is severe bacterial infections observed in the early childhood which start from the delivery. There is severe neutropenia; the neutrophil count is below  $200/\text{mm}^3$ . The incidence is 12/1 000 000 and the female/male ratio is equal.

# 1. Kostmann syndrome

Although it generally has an autosomal recessive inheritance, it may also occur as a result of autosomal dominant inheritance or spontaneous mutations. Mutations in the neutrophil elastase gene are responsible of this syndrome. These mutations stop maturation in the promyelocyte/myelocyte stage in the bone marrow.

# 1. Kostmann syndrome

Clinically, severe bacterial infections including omphalitis, otitis, pneumonia, sepsis and cutaneous and hepatic abscesses are found. If these infections are not treated, they threaten life and the most commonly found agents include staphylococci, streptococci, gram negative bacilli and fungi..

# 1. Kostmann syndrome

The disease becomes symptomatic in the first month in 50% of the cases and in the first six months in 100% of the cases.

More than 95% of the patients give response to low dose (3–10  $\mu\text{g}/\text{kg}$ ) G-CSF.

# 1. Kostmann syndrome

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# 1. Kostmann syndrome

Granulocyte colony stimulating factor increases the number of neutrophils and decreases the frequency of infections by correcting the pause in maturation of myelocytes. The patients are not lost because of infection. If they survive, G-CSF receptor mutations occur in 12% and cytogenetic changes including monosomia 7 occur in 50%.

# 1. Kostmann syndrome

In presence of cytogenetic changes, these patients carry a risk of malignant transformation (myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML)). Bone marrow transplantation should be performed in the patients who are unresponsive to granulocyte colony stimulating factor.

# 1. Kostmann syndrome

If bone marrow transplantation is to be performed, it should be performed in the neutropenic period. It is emphasized that the success rate is very low, when it is performed after malignant disease develops.

# 1. Kostmann syndrome

It is known that the risk of development of MDS and AML is high in patients who receive a daily G-CSF dose above 8  $\mu\text{g}/\text{kg}$ . Although a relation between malignant transformation and use of G-CSF is suspected, it is rather interpreted such that it is related with a decrease in losses due to infection and occurrence in this group of patients who can live up to advanced ages

## 2. Cyclic neutropenia

Cyclic neutropenia is characterized with fever, painful oral ulcers, lymphadenopathy and recurrent infections which develop in relation with recurrent severe neutropenia. It has an autosomal dominant inheritance and the mutations in the neutrophil elastase gene are responsible of this disease similar to Kostman syndrome. These mutations cause to neutropenia by accelerating apoptosis in neutrophil precursors .

## 2. Cyclic neutropenia

Cyclic neutropenia generally occurs below the age of one year. Fever, oral ulcers, lymphadenopathy and severe neutropenia occur every 21 days (14–42 days) as regular attacks. The attacks generally last for 3–6 days and patients are asymptomatic during the intervals and the neutrophil counts are normal .

## 2. Cyclic neutropenia

Most patients can be followed up by reducing the problems using low dose G-CSF. The interval between the attacks prolongs and the period of neutropenia shortens with granulocyte colony stimulating factor

### 3. Shwachman-Diamond syndrome

This syndrome which generally becomes symptomatic during infancy is characterized with autosomal recessive exocrine pancreatic failure, short stature, developmental retardation, immune disorder, hepatic disease, skeletal abnormalities and hematological involvement.

### 3. Shwachman-Diamond syndrome

Its incidence ranges between 1/100 000 and 1/200 000. It is more common in males.

Pancreatic failure (steatorrhea, malabsorption) is observed in addition to neutropenia which is specific for the syndrome. In addition, growth and developmental retardation and skeletal abnormalities in the form of metaphyseal dysplasia may be found.

### 3. Shwachman-Diamond syndrome

Anemia, increased HbF level, thrombocytopenia, disrupted neutrophil chemotaxis may be observed in addition to neutropenia. These patients should be monitored closely. Malign diseases may be found in the follow-up.

### 3. Shwachman-Diamond syndrome

Oral pancreatic enzymes are used for pancreatic failure, cyclosporin A is used for bone marrow failure and G-CSF is used for deep neutropenia. Bone marrow transplantation should be performed as soon as possible

## 4. Myelokathexis

This is a rare cause of severe neutropenia which has an autosomal dominant inheritance.

Disruption occurs in neutrophils in the bone marrow as a result of decreased expression of Bclx which is an antiapoptotic protein and release of these cells into the peripheral blood is disrupted (ineffective myelopoiesis)

## 4. Myelokathexis

Use of granulocyte colony stimulating factor may increase the neutrophil count. It has a form which is abbreviated as WHIM (Warts, Hypogammaglobulinemia, Infections, Myelokathexis). Extensive warts, hypogammaglobulinemia, infections and myelokathexis are found in this syndrome

## 5. Reticular dysgenesis

Reticular dysgenesis is disruption in undifferentiated stem cells; none of the myeloid cells can be produced. Erythrocyte and platelet production is normal. Agranulocytosis and lymphoid hypoplasia are present. Abnormal T cells and a marked reduction in IgA and IgM levels are observed.

## 5. Reticular dysgenesis

The bone marrow is hypoplastic. The patients are lost in early infancy because of severe bacterial infections. The only treatment method is bone marrow transplantation in the early stage

## 6. Dyskeratosis congenita

This is a X-linked disease characterized with bone marrow hypoplasia, mild neutropenia, nail dystrophy and cutaneous reticular hyperpigmentation. Neutropenia is mild and infections are rare

## 7. Neutropenia related with immunological disorders

Neutropenia may accompany many immune deficiencies (gammaglobulin abnormalities, T cell defects, natural killer cell abnormalities). These patients generally present with recurrent bacterial infections, hepatosplenomegaly and developmental retardation in childhood.

## 7. Neutropenia related with immunological disorders

Since consanguineous marriages are common in Turkey, there is a history of similar disease in the family. Neutropenia is observed with a rate of 25% in X-linked agammaglobulinemia and with a rate of 50% in X-linked hyperimmune M syndrome.

## 7. Neutropenia related with immunological disorders

The cause of neutropenia in immune deficiency syndromes has not been elucidated fully. Mostly, decreased production and autoimmune mechanisms are blamed. In hyperimmune M syndrome, it is thought that G-CSF production is not triggered because of disrupted CD40 ligand on the surface of B lymphocytes and this leads to neutropenia. Treatment should be directed to the primary disease rather than neutropenia

## 8. Neutropenia related with metabolic diseases

Neutropenia is observed in congenital metabolic diseases including hyperglycinuria, orotic aciduria, methylmalonic aciduria, hyperglycinemia and more commonly glycogen storage disease (GSD) type 1b patients.

## 8. Neutropenia related with metabolic diseases

In glycogen storage disease, hypoglycemia, convulsions and hepatosplenomegaly are observed in relation with disruption in glucose-6-phosphate translocase enzyme. In glycogen storage disease type 1b, neutropenia and neutrophil dysfunction are present in contrast to the other types.

## 8. Neutropenia related with metabolic diseases

Although the cause of neutropenia and neutrophil dysfunction is not known clearly, maturation pause in the myelocyte stage in the bone marrow may be observed. In some patients, there is problem in release of neutrophils into the peripheral blood. G-CSF is used in treatment, but it should be kept in mind that hypersplenism requiring splenectomy may occur in long-term use

## 9. Other causes

Rarely, isolated neutropenia may be observed in the initial phase of bone marrow failure syndromes involving the whole bone marrow. Afterwards, other series may be affected.

# Evaluation of neutropenic patients

In evaluation of the patients, neutropenia should be confirmed primarily. When a neutropenic blood count is found, blood count is repeated on the blood sample which is ensured to have been obtained under appropriate conditions and not kept waiting, using a qualified automation device. Examination should be performed after neutropenia is confirmed with peripheral smear.

# Evaluation of neutropenic patients

In addition, findings directed to specific diagnoses should be evaluated with peripheral smear. For example, presence of **blasts** suggests leukemia, **nucleated erythrocytes** suggest hemolytic anemia or blood loss, **hypersegmented neutrophils** suggest vitamin B12 or folic acid deficiency and neutrophils with **pycnotic nuclei** suggest myelodysplasia.

# Evaluation of neutropenic patients

The tables which show standard neutrophil counts by age should be referred to in order to confirm neutropenia. Generally, repetitive blood counts are performed to exclude transient neutropenia observed in viral infections in young children.

# Evaluation of neutropenic patients

Neutropenia may also rarely be found as a result of relative reduction in the peripheral blood because of adhesion of neutrophils onto the vascular wall or hiding in the spleen and bone marrow. Two different tests are performed to demonstrate these situations :

1. Neutrophil reserve in the vascular wall
2. Bone marrow neutrophil reserve

# 1. Neutrophil reserve in the vascular wall

Epinephrine (adrenaline) test (0.1 mL 1: 1 000 sc): the absolute neutrophil count is measured at the 5th, 10th, 15th and 30th minutes.

Normal: increase of the figure by two-fold.

## 2. Bone marrow neutrophil reserve

**1) Cortisone stimulation test (5 mg/kg IV):** The absolute neutrophil count is measured every hour for 6 hours. Normal: An increase of  $2\ 000/\text{mm}^3$  in the neutrophil count.

**2) Typhoid stimulation test (0.5 mL vaccine s.c) (currently not performed frequently):** The absolute neutrophil count is measured at the 3<sup>rd</sup>, 6<sup>th</sup>, 12<sup>th</sup> and 24<sup>th</sup> hours. Normal: A 3-4-fold increase is expected in the absolute neutrophil count.



A detailed history including the time of onset of neutropenia, the severity and frequency of infection, presence of recurrent infections, medications used and unexplained infant deaths in the family should be taken.

On physical examination, growth and development retardation, phenotypical abnormalities and findings of infection should be noted. The mucous membranes, gingiva, teeth, skin, tympanic membranes, perianal region, liver, spleen and lymph nodes and nail bed and surroundings should specifically be examined carefully and the family should be taught to regularly check these regions.

In presence of petechiae and purpura, thrombocytopenia should be suspected and systemic diseases should be considered. Presence of rheumatic findings should be investigated.

The severity and duration of neutropenia determine the extent of laboratory studies. If the patient is found to be neutropenic during viral infection or a short time after viral infection, complete blood count should be repeated 2–4 weeks later. Generally, neutropenia improves during this period and examination of bone marrow is not needed. However, neutropenias which develop secondary to infection rarely last for longer than eight weeks and may persist for up to one year.

Patients with a history of recurrent severe infections secondary to neutropenia should be investigated in detail. In the early phase, it is sometimes difficult to understand if neutropenia has caused to infection or infection has caused to neutropenia

**Complete blood count** is performed 2–3 times a week for six weeks to differentiate cyclic neutropenia from severe chronic neutropenia.

**Bone marrow aspiration** and **cytogenetic** examination are needed both for identification of myeloid cell maturation and for the diagnosis of myelodysplastic syndrome and leukemia.

Patients who have **diarrhea or malabsorption** together with neutropenia should be examined in terms of Shwachman-Diamond syndrome.

**Growth and development** should be closely monitored in children with recurrent infections caused by chronic severe neutropenia. **ANA** should be tested in patients with findings of rheumatic disease and **vitamin B12 and folic acid** levels should be measured in patients with malnutrition. Neutropenic patients with recurrent infections and a **familial history** of sibling death should definitely be evaluated in terms of immune deficiency.

If the cause of neutropenia is HAX gene mutation, neurological problems are present in 30% of the cases (epileptic seizures, learning difficulty, developmental disorder)

Tests to be ordered in neutropenic patients: **one should not hurry to order tests for neutropenic patients.** The clinical picture should always be directive for investigations. In case of severe, recurrent infections, acting quickly can sometimes save the patient's life. It should be kept in mind that the majority of neutropenias in the childhood are secondary **to infection** and the tests are expensive and not available everywhere clinics

History of drug use should be taken carefully in neutropenic patients and patients should be followed up for at least two months after discontinuing all drugs, if possible. Follow-up should not be discontinued quickly in neutropenic patients. One should be careful in terms of MDS and leukemia, but this should not be shared much with the family. Otherwise, we can create a hypochondriac patient group who have their complete blood counts performed almost every day in outpatient clinics

# Laboratory tests:

**Complete blood count**, absolute neutrophil count and reticulocyte count

A 6–8 week chart, three times a week to exclude cyclic neutropenia

Maturation stages and pausing in the granulocyte series should be noted on **bone marrow examination**

# Laboratory tests:

**Karyotype and FISH** should be studied on bone marrow samples in terms of the risk of development of MDS and leukemia (especially monosomia 7 and 5q)

Electron microscopic examination

Identification of antineutrophil antibody

# Laboratory tests:

- Identification of antineutrophil antibody
- Granulocyte immunofluorescence test (GIFT)
- Granulocyte indirect immunofluorescence test (GIIFT)
- Granulocyte agglutination test (GAT)
- Enzyme-linked immunoassay (ELISA)
- Monoclonal Antibody Immobilization of Granulocyte Antigens (MAIGA)

# Laboratory tests:

Immunological tests

Immunoglobulins (IgA, IgG, IgM, IgE)

Cellular immunity (lymphocyte subgroups T cell proliferation, T cell subgroup examination, NK counts and function skin tests, purified protein derivative (PPD) test)

Antinuclear antibodies, C3, C4, CH50

# Screening for metabolic diseases

1) Amino acid screening in plasma and urine

2) Serum vitamin B12, folic acid and copper levels

## Findings of pancreatic disease

1) Findings of exocrine pancreatic failure:  
fecal fat, pancreatic enzyme, serum  
trypsinogen and isoamylase levels

2) Evaluation of the pancreas in terms of  
lipomatosis with computerized tomography

10) Identification of chromosome breakage  
(specifies Fanconi anemia)

11) Bone graphies (cartilage-hair hypoplasia,  
Shwachman-Diamond syndrome, Fanconi  
anemia)

12) Serum muramidase level (indicates ineffective  
myelopoiesis)

13) Flow cytometry examination CD55 and CD59  
(PNH disease)

14) Bone density measurement (osteoporosis and osteopenia are present in 14% of neutropenic patients)

15) Gene mutation examinations (ELA2, GFI-1, WAS, SBDS (Shwachman-Diamond syndrome), HAX1, TAZ (Barth syndrome), Fanconi genes, LYST (Chediak Higashi syndrome), G6PC3 deficiency)

# Treatment and use of G-CSF in chronic neutropenias

Satisfactory outcomes could be obtained after introduction of G-CSF in chronic neutropenias. Only antibiotics and lithium derivatives had been used previously and a good clinical response could not be observed. The results of international severe chronic neutropenia records found that the neutrophil count became normal, infections could be prevented and the symptoms of inflammation decreased in more than 90% of the patients using G-CSF.

# Treatment and use of G-CSF in chronic neutropenias

In congenital neutropenia, a good response was obtained with a higher dose. In the idiopathic group, response could be obtained with lower doses. Unresponsive patients constitute a small group of the patients with congenital neutropenia and they are lost, if early bone marrow transplantation (BMT) is not performed. These drugs which stimulate neutrophil production in the bone marrow are administered subcutaneously at an appropriate dose with appropriate intervals.

# Treatment and use of G-CSF in chronic neutropenias

They may cause to side effects including fever, shivering and muscle and bone pain. Since these side effects are observed only in the beginning of treatment, they do not cause to problems in treatment compliance. As emphasized in the part of Kostmann syndrome, the claims that G-CSF treatment causes to malignant transformation especially in patients with congenital neutropenia constitute the side effect which is discussed to the greatest extent. of  $>8\mu\text{g}/\text{kg}/\text{day}$

# Treatment and use of G-CSF in chronic neutropenias

The survival times of patients with chronic neutropenia have prolonged with granulocyte colony stimulating factor. As a result, the thought that G-CSF saves time for development of malignancy predominates. In this patient group, G-CSF also improves the quality of life by markedly decreasing infections in addition to increased survival time. of  $>8\mu\text{g}/\text{kg}/\text{day}$

# Treatment and use of G-CSF in chronic neutropenias

The risk of MDS/leukemia was found to be 11.8% in patients (50/422) with severe neutropenia who had been followed up between 1987 and 2005.

Again, the annual risk of development of MDS/leukemia was found to be 2% in 374 patients who had been using G-CSF for at least ten years in another study. In these patients, the risk of development of MDS/leukemia was found to be 22% 15 years later. The risk is higher in patients with a ANC of  $<2.1 \times 10^9/L$  despite use of a dose of  $>8 \mu g/kg/day$

# When you have a neutropenic patient;

- Hospitalize the patient if he/she looks toxic and has a body temperature persisting above 37.5 °C.
- Obtain cultures immediately (especially hemoculture, urine culture, throat culture and culture of infected area, if present).
- Initiate a wide spectrum antibiotic by the intravenous or intramuscular route (should have strong gram negative efficiency).

# When you have a neutropenic patient;

- If microorganism is grown in culture, antibiotic treatment is continued for 10–14 days by the intravenous route.
- If no microorganism is grown in culture, continue antibiotic treatment until fever subsides and neutropenia improves (this condition may not be valid for patients who are known to have neutropenia previously).
-

# When you have a neutropenic patient;

- Put the patient in a single room, if possible or in accompaniment with another patient who is known to have no infection for sure.
- Limit entry of guests and other healthcare workers.
- Be sure that people entering the room have washed their hands.
- Clean the skin surface with povidone or chlorhexidine solution before each intervention.

# When you have a neutropenic patient;

- Avoid interventions by way of oral mucosa, perineum and rectum (rectal temperature measurement, enema and rectal palpation should be avoided).
- Administer antibiotic to prevent development of secondary bacterial infections in presence of oral ulcers and gingivitis, make the patient rinse his/her mouth with 3% hydrogen peroxide and make him/her use a soft toothbrush.
- If the patient has a diagnosis (especially Kostmann, Schwachman-Diamond or severe

# When you have a neutropenic patient;

- Avoid interventions by way of oral mucosa, perineum and rectum (rectal temperature measurement, enema and rectal palpation should be avoided).
- Administer antibiotic to prevent development of secondary bacterial infections in presence of oral ulcers and gingivitis, make the patient rinse his/her mouth with 3% hydrogen peroxide and make him/her use a soft toothbrush.

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- If the patient has a diagnosis (especially Kostmann, Shwachman-Diamond or severe neutropenia), initiate G-CSF at a dose of 5  $\mu\text{g}/\text{kg}$  and increase the dose rapidly by the neutrophil count.

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Until the present time, a total of 19 gene defects including 7 gene mutations leading to congenital neutropenia (ELANE; CXCR4, SBDS, PT14, HAX1, G6PC3, RUNX1) and different genetic diseases accompanied by neutropenias have been identified

**JAGN-1** deficiency which has been very recently identified is also one of the causes of severe neutropenia. It has autosomal recessive inheritance and adequate increase in the neutrophil count is not found with G-CSF treatment. Since **RUNX1** and **CSF3R** mutations among congenital neutropenias carry a potential for leukemia, G-CSF should be used carefully in patients with these mutations.

In addition, patients who have ELANE, SDS or GATA2 mutation also carry a risk for development of leukemia

ELANE gene mutation may present with a picture of both cyclic neutropenia and congenital neutropenia. AML/MDS does not develop in patients with a clinical picture of cyclic neutropenia, whereas AML/MDS is found with a rate of 15% in patients with a picture of congenital neutropenia .

In congenital neutropenia, the factors which determine the risk of leukemia include the **neutrophil count, mutation type** and intensity of **G-CSF treatment**. It is showed that, use of vitamin B3 (niacin) and G-CSF in treatment of severe congenital neutropenia as a novelty increased neutrophil count significantly at the end of four weeks

New immune deficiency syndromes have been found in recent years while elucidating the etiology of neutropenia in the light of genetic examinations. In DOCK2 and DOCK8 deficiencies, invasive bacterial and viral infections are observed starting from early ages.

Increased IgE, allergy and fungal infections are more frequent especially in DOCK-8 deficiency, while lymphopenia, disrupted antibody response, natural killer cell and neutrophil dysfunction are more prominent in DOCK2 deficiency. This disease can be healed completely with bone marrow transplantation