Neutrophil disorders

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IMMUNO DEFICIENCY UK

Supporting families affected by primary and secondary immunodeficiency

About this leaflet

This leaflet is designed to help answer some of the questions that families may have about the immune conditions known as neutrophil disorders. It has been produced with the kind help of Dr Tasmeen Rahman and approved by the Immunodeficiency UK Medical Advisory Panel and Patient Representative Panel.

The information contained in this leaflet should not replace advice from a clinical immunologist or a geneticist.

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Summary

Neutrophil disorders are a group of conditions that affect the body's ability to fight bacterial and fungal infections. Neutrophils are a type of white blood cell that clear bacteria and fungi from the body. They are also called granulocytes or pus cells.

Neutrophils are produced in bone marrow and released into the blood. They control infection by travelling into body tissues to kill microorganisms, such as bacteria and fungi. Neutrophils destroy bacteria and fungi through a process called phagocytosis. This process involves the neutrophils engulfing infected cells and using granules (small particles) and chemicals to destroy the bacteria and fungi. Neutrophils also produce chemical signals that attract other neutrophils at sites of infection, and an accumulation of neutrophils forms pus.

There are many different conditions that are grouped under the heading neutrophil disorders. However, people affected by a neutrophil disorder have:

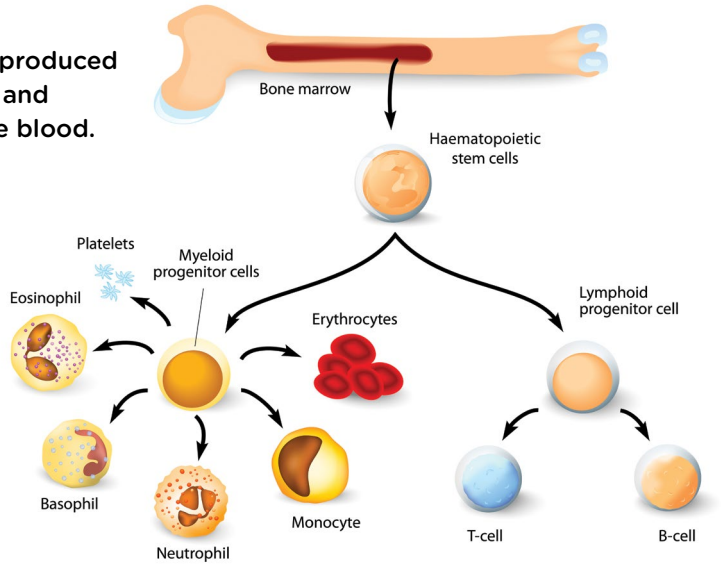
- a reduced number of neutrophils, owing to a defect in the production of neutrophils, or
- neutrophils that don't function properly, or
- low numbers of neutrophils, associated with another disorder.

If you have a neutrophil disorder it means that you can't fight infections as well as people with normal levels of functioning neutrophils. Some neutrophil disorders affect both males and females, and the severity of the condition can vary. From an early age, patients may have severe, recurrent bacterial and fungal infections, such as pneumonia, meningitis, sepsis and abscesses.

The aim of treatment is to reduce the risk of infection by practising good hygiene, including dental hygiene and skin care, and to treat promptly any infections with antibiotics and antifungal agents. More specialised treatments depend on the condition and may include stimulation of the bone marrow to produce more neutrophils (using G-CSF ((granulocyte colony-stimulating factor) injections) and, if appropriate, a stem cell transplant.

The outlook for patients with neutrophil disorders depends on the severity of the disease, how much damage has occurred before diagnosis and how successfully infections can be prevented and treated in the future.

Neutrophils are produced in bone marrow and released into the blood.



How did I get a neutrophil disorder?

There are two common causes of low numbers of neutrophils (neutropenia). The first is chemotherapy given to patients in the treatment of cancer. The second is an autoimmune condition, such as lupus. Neutrophil disorders caused by an autoimmune condition are called autoimmune neutropenias, owing to the body producing antibodies to its own neutrophils, or to the bone marrow stem cells from which neutrophils are derived.

This leaflet focuses on inherited genetic conditions that affect the production of neutrophils or the way neutrophils work (see Table 1). These conditions come under the heading primary immunodeficiencies and can be passed down from one generation to the next.

Some types of neutrophil disorders can be inherited from one parent who has a faulty gene. Other types of neutrophil disorders are inherited only if both parents have a faulty gene. Further types are X-linked, which means that the condition usually affects males only.

The faulty genes can affect the production or the function of neutrophils. The way the genes are inherited often means that the parents are themselves unaffected. This has implications for family planning, and families may need genetic counselling.

Immunodeficiency UK has a separate leaflet devoted to the genetics of primary immunodeficiency; available at **www.immunodeficiencyuk.org**.

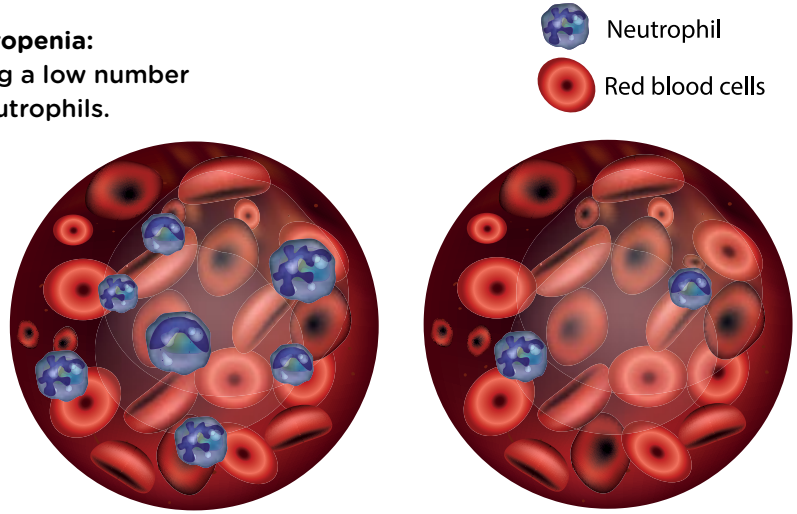
Table 1. Types of neutrophil disorders and their inheritance

Disorders causing low numbers of neutrophils	**Brief description**	**Inheritance pattern**
Kostmann syndrome, also known as severe congenital neutropenia (SCN)	Inherited defect in neutrophil production. Causes recurrent infection in very early life.	Autosomal recessive
Cyclic neutropenia	Low neutrophil numbers occur every two to four weeks.	Autosomal dominant
G-CSF receptor deficiency	G-CSF is a chemical that stimulates neutrophil production by binding to the receptor on the cell's surface. Faulty genes can cause the receptor not to work properly, resulting in low numbers of circulating neutrophils.	Autosomal recessive
X-linked neutropenia	A genetic defect in the Wiskott Aldrich (WAS) gene. This genetic variant causes the WAS gene to be activated and affects normal neutrophil development in the bone marrow. Despite often severe neutropenia, infections are usually mild.	X-linked
Disorders where the neutrophil function is affected	**Brief description**	**Inheritance pattern**
*Chronic granulomatous disorder (CGD)	An inability to kill microorganisms owing to genetic faults in distinct parts of a key enzyme important for the killing of bacteria and fungi.	X-linked Autosomal recessive
Leukocyte adhesion deficiencies (LAD-1, 2 and 3)	An inability of neutrophils to exit the bloodstream and enter tissues to kill microorganisms. This is due to defects in the way neutrophils recognise, adhere and move through blood vessel walls.	Autosomal recessive
Rac2 deficiency	Rac2 is an important part of an enzyme critical in the killing of microorganisms.	Autosomal recessive
Specific granule deficiency	Unable to kill microorganisms effectively owing to a decrease in the number or function of neutrophil granules, which produce toxic materials and enzymes to kill bacteria and fungi.	Autosomal recessive

*Further information on CGD can be found at **www.cgdsociety.org**

Several other primary immunodeficiency conditions may be associated with low neutrophil numbers.

Neutropenia:
having a low number of neutrophils.



Normal blood cells **Neutropenia**

What are the symptoms of neutrophil disorders?

Symptoms often occur from a young age and include recurrent and often severe bacterial and fungal infections. Bacteria (such as Staphylococcus, E. coli, Serratia and Klebsiella) and fungi (such as Candida and Aspergillus) cause the most common infections. Repeated infections can cause a child to have delayed growth and development. Unusual, atypical infections with mycobacteria (related to the tuberculosis organism) may occur in some patients.

Common features, which you may recognise in yourself or your child, include:

- Skin and surface tissues – abscesses, cellulitis, infected lymph nodes, infected belly button (umbilicus), poor wound healing, fungal infections (including persistent thrush and fungal rashes).
- Mouth – ulcers, gingivitis, dental abscesses, stomatitis (inflammation of the mouth and lips).
- Lungs – pneumonia, abscesses, bronchiectasis.
- Gut – colitis, inflammatory bowel disease, diarrhoea, liver abscesses, peri-anal abscesses, inflammation of the caecum (typhlitis).
- Blood – in addition to infections, other symptoms can include anaemia, and bleeding and bruising tendencies, and can sometimes be associated with types of leukaemia.

How are neutrophil disorders diagnosed?

Recurrent infections will lead a doctor to look for underlying causes, but as infections are common at any age, the clues may not always be apparent. A clinical history of severe, recurrent infections, a possible family history of immune deficiency and slowing of growth or development are important factors to consider. A careful physical examination will also alert the doctor to the possibility of a neutrophil disorder, which can be confirmed by the following tests:

- A full blood count (FBC) – to measure the numbers of neutrophils and other white blood cells, plus red blood cells, platelets and haemoglobin. Repeat tests are often necessary as sometimes the neutropenia occurs in cycles
- Autoimmune tests – to look for evidence of autoimmune diseases which may explain neutropenia
- Tests for specific autoantibodies against neutrophils
- Specialist genetic tests – to see which genes may be affected
- Microbiology tests – to look for the specific organism causing an infection. This involves taking samples of body fluids including sputum, stools, skin and throat/nasal swabs
- Bone marrow biopsy – a sample of bone marrow is usually taken from the top of the pelvic bone, just below the waist, using a thick needle. A local anaesthetic and a sedative are often given to minimise any discomfort.

Further tests may include X-rays and scans (e.g. chest X-rays, ultrasound scans, CT scans) depending on which part of the body is affected.

Treatment

The priority is to treat any serious bacterial or fungal infections with antibiotics or antifungal medicines. Some people need to take prophylactic medicines – a regular dose to prevent infections from flaring up.

Other preventative measures are good skin and dental hygiene, and constant vigilance for signs of infection. Regular dental checks are important, and your dentist should be made aware of your condition. Please see the Immunodeficiency UK leaflet, *Keeping well and healthy when you have a PID* available on our website at **www.immunodeficiencyuk.org**.

Infections should be treated promptly and vigorously, and your GP should be aware of this.

Where the number of neutrophils is low, injections of G-CSF are given under the skin to stimulate the bone marrow to produce and release neutrophils.

Haematopoietic stem cell transplant (HSCT), also known as a bone marrow transplant (BMT), can offer a permanent cure for those with inherited disease which does not respond to G-CSF injections. Ideally, HSCT is carried out before the cycles of repeated infection and inflammation take their toll on the body. Further information about what is involved in having an HSCT/BMT and its risks will be provided by the BMT centre. Families will have a chance to discuss this treatment option in detail with an immunologist and BMT consultant on several occasions.

Gene therapy aims to correct the underlying genetic abnormality by replacing the faulty gene in immune cells with a normal copy. It is currently undergoing clinical trials in selected patients who have certain neutrophil disorders, including CGD and LAD.

Additional treatments may be required for those with complications. If lung problems, such as bronchiectasis, have developed, then physiotherapy may be needed to remove excess mucus from the airways.

A healthy diet is important and advice from a dietician may be advisable, especially if you have gut symptoms.

It is important not to smoke. If you are a smoker, then your GP can offer support for you to stop smoking.

How will my health be monitored?

You will usually be under the care of an immunology team comprising doctors and specialist nurses. Monitoring is by regular appointments, blood tests and involvement of other specialists if necessary. It is a good idea to note down any concerns and questions you may have before each appointment.

Please see the Immunodeficiency UK leaflet, *Making the most of your appointments* available on our website at **www.immunodeficiencyuk.org**.

What does this mean for the future?

Without treatment, patients remain at risk of serious infections and inflammation. With HSCT, people with inherited neutrophil disorders can be cured and live a normal life.

If the condition is inherited, then you and your family may be offered genetic counselling. Genetic counselling both for affected people and for family members is important once the genetic cause is known.

Immunisation

Not all vaccines are safe to be given to people with neutrophil disorders. You should discuss any recommended vaccinations with your immunology team before receiving a vaccine.

Is there a support group?

Immunodeficiency UK is the main support organisation in the UK for anyone affected by a primary or secondary immunodeficiency condition. Call our helpline on 0800 987 8986 or visit our website at **www.immunodeficiencyuk.org**.

The Chronic Granulomatous Disorder Society (CGD Society) is the support group for people affected by CGD. Its website is at **www.cgdsociety.org**

Reference

Neutrophil disorders and their management.
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Glossary of terms

abscess a collection of pus that has built up in a tissue of the body.

anaemia a condition resulting from having fewer red blood cells than normal or where each red blood cell has less haemoglobin in it than normal. It results in tiredness.

antibiotics drugs used to treat or prevent some types of bacterial infection. They work by killing bacteria or preventing them from spreading.

antibody a type of protein (immunoglobulin) that is produced by certain types of white blood cells (plasma cells – a type of B-cell). The role of antibodies is to fight bacteria, viruses, toxins and other substances foreign to the body.

antifungal agent a medicine used to treat infections caused by fungi.

autoantibodies antibodies that attack the body's own tissues.

autoimmune/autoimmunity when an individual's immune system attacks the body's own tissues or vessels.

autosomal dominant a type of inheritance. If a faulty gene is dominant, it will show an effect even though there is a working copy of the gene on the other chromosome. A person only needs to inherit one faulty gene from one parent to develop a disease in a dominantly inherited condition. The risk of having a child with the condition is 50 per cent (or 1 in 2) for each pregnancy.

autosomal recessive a type of inheritance where the presence of one copy of a faulty gene does not affect the individual him or herself. However, when two carriers of the same faulty gene have children, there is a 25 per cent (or 1 in 4) chance of a child inheriting two copies of the faulty gene (one from each parent) for each pregnancy. If this happens, the child is affected by the disorder.

bacteria very small germs that are found everywhere and are the cause of many diseases.

biopsy a procedure to remove a piece of tissue or a sample of cells from your body so that it can be studied in a laboratory.

bone marrow soft, spongy tissue located in the hollow centres of most bones; it contains developing blood cells and cells of the immune system.

bone marrow transplantation (BMT) the transfer of bone marrow, obtained by aspiration usually from the hip bones, from a donor – either related or unrelated – to a recipient. The donor bone marrow replaces the recipient's bone marrow, giving the recipient a new immune system and curing the immunodeficiency (see also haematopoietic stem cell transplantation).

bronchiectasis a widening of the tubes (bronchi) that lead to the air sacs of the lung; this can happen because of repeated bouts of infections.

cellulitis a bacterial infection involving the inner layers of the skin.

CT scan also known as a CAT scan. A specialised X-ray that gives pictures of the inside of the body.

deficiency a lack or shortage.

fungi members of a class of relatively primitive microorganisms, including mushrooms, yeasts and moulds. Fungal infections can be particularly serious in people with primary immune deficiency.

G-CSF granulocyte colony-stimulating factor is given by injection to stimulate the bone marrow to produce neutrophils.

gene the fundamental unit of inheritance that carries the instructions for how the body grows and develops. Autosomal dominant/autosomal recessive/X-linked are all ways in which genes are inherited.

gene therapy attempting to cure genetic diseases by placing a normal 'healthy' gene into cells that have a faulty version of that gene.

genetic counselling a service that provides information and advice about genetic conditions to people and their families to help with family planning.

gingivitis/stomatitis infection or inflammation of the gums and mouth.

haematopoietic stem cells cells from which all blood cells and immune cells are derived.

haematopoietic stem cell transplantation (HSCT) the transfer of bone marrow (obtained by a medical procedure) or stem cells (obtained from blood or stored umbilical cord blood) from a donor – either related or unrelated – to a recipient. Haematopoietic means blood-forming. The donor cells are given by intravenous infusion and make their way to the recipient's bone marrow to provide a new immune system, curing the immunodeficiency.

haemoglobin an iron-rich protein in red blood cells. It carries oxygen to the tissues in the blood.

immune deficiency when the immune system's ability to fight infectious disease is compromised or entirely absent.

inheritance the passing down of genetic information from parents to children. Autosomal dominant, autosomal recessive and X-linked are all types of inheritance.

lymph nodes small bean-sized organs of the immune system that are distributed widely throughout the body. They are the home for the many types of cells that are important in fighting infections.

meningitis an infection of the meninges (protective membranes) that surround the brain and spinal cord. The infection can be bacterial, viral, tuberculous or inflammatory (non-infectious).

mycobacteria a type of bacteria.

phagocyte a type of white blood cell that protects the body by eating (phagocytosing) dirt, bacteria and dead or dying cells.

phlegm mucus from the lungs.

platelet a blood cell that works to prevent bleeding in the body by producing blood clots.

pneumonia a swelling (inflammation) of the tissue in one or both lungs. It is usually caused by an infection.

prophylactic/prophylaxis something that works to defend or protect against disease.

pus a liquid, typically white–yellow, yellow or yellow–brown, formed at the site of inflammation during bacterial or fungal infection.

sepsis a common and potentially life-threatening condition triggered by an infection.

ultrasound scan a procedure that uses high-frequency sound waves to create an image of part of the inside of the body.

X-linked refers to the inheritance of disorders caused by mutations in genes carried on the X (or female sex) chromosome. This is also known as sex-linked inheritance. In this situation, girls are usually carriers and boys are affected by the condition. Girls inherit one X chromosome from each parent, so have a normal one to compensate for the faulty one. Boys inherit one X chromosome and one Y chromosome, so the effects of the faulty X chromosome are not cancelled out.

Notes

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About Immunodeficiency UK

Immunodeficiency UK is a national organisation supporting individuals and families affected by primary and secondary immunodeficiency.

We are the UK national member of IPOPI, an association of national patient organisations dedicated to improving awareness, access to early diagnosis and optimal treatments for PID patients worldwide.

Our website has useful information on a range of conditions and topics, and explains the work we do to ensure the voice of patients with primary and secondary immunodeficiency is heard. If we can be of any help, please email us or call on the number above, where you can leave a message.

Support us by becoming a member of Immunodeficiency UK. It's free and easy to do via our website. Members get monthly bulletins.

Immunodeficiency UK is reliant on voluntary donations. To make a donation, please go to **www.immunodeficiencyuk.org/donate**

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Supporting families affected by primary and secondary immunodeficiency

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