

## NEUTROPENIA: AN EXPLANATORY GUIDE FOR PARENTS AND REFERRING PHYSICIANS

**What is neutropenia?** Neutropenia is a reduction in the number of circulating blood neutrophils, a form of white blood cell important in preventing and combating infection due to many types of bacteria (germs).

**Where are neutrophils made and how do they work?** Neutrophils (which are also called granulocytes, polys, segs, or segmented leukocytes) are manufactured in the bone marrow, the spongy fatty tissue inside the bones. Neutrophils are produced there along with red blood cells (that carry oxygen) and platelets (small sticky elements that help the blood to clot). The bone marrow produces millions of neutrophils every day. The neutrophils then enter the bloodstream, circulate for a few hours, and enter the tissues of the body (skin, mouth, intestines, lungs, etc.) to identify and destroy germs. Neutrophils actually attack, eat, and digest the bacterial germs. Neutrophils are extremely important in the body's defense against infection. Thus, neutropenia – a deficiency of neutrophils in the blood – can be a serious problem.

**How are neutrophils counted and what is the normal neutrophil count?** Neutrophils are included as part of the complete blood count (or CBC) performed on blood obtained by a fingerstick or puncture of a vein in the arm. It is a fairly simple test that can be done in almost any medical laboratory. The percentage and number of neutrophils in the blood is usually included as part of the differential white blood cell (WBC) count (or “diff”). The neutrophils normally constitute between 30% and 70% of the white blood cells. The other types of white blood cells (called lymphocytes, monocytes, eosinophils, and basophils) are not as important in fighting bacteria.

The total WBC count in infants and children are normally between 4,000 and 15,000 cells per cubic millimeter of blood. The neutrophil count is expressed either as a percentage of the total white blood cells or as the absolute neutrophil count (ANC). The ANC is calculated by multiplying the percentage of neutrophils in the blood times the total WBC count. (Examples: A normal child might have a WBC count of 8,000 with 40% neutrophils; therefore the ANC is  $.40 \times 8,000 = 3,200$  per cubic millimeter. A child with neutropenia might have a WBC count of 4,000 with 5% neutrophils; in this case, the ANC is  $.05 \times 4,000 = 200$  per cubic millimeter).

**What is considered a low ANC value?** Normally the ANC is above 1500 (1000 in children less than 2 years of age). Mild neutropenia (ANC 500 to 1000 or 1500) is usually not a problem. When the ANC is less than 500, more infections than usual can occur (see below). African-American children have lower ANCs than Caucasians. As indicated below, minor viral infections can sometimes transiently (for a week or two) cause the ANC to drop even lower.

**What are bands?** Bands are “baby” neutrophils that are sometimes noted on blood count reports. They are usually counted along with the neutrophils (or polys or segs) when calculating the ANC. A marked elevation in the percentage of bands is often seen with bacterial infection.

**What happens when the neutrophils (ANC) are low?** A low neutrophil count may cause an increased risk of bacterial infection. In most cases, these infections are minor, including ear infections (otitis media), pharyngitis (throat infections), skin boils, mouth sores, inflamed gums, and urinary tract infections. However, sometimes, especially when the ANC is extremely low (under 200), serious and even life-threatening infections may occur. These dangerous infections include pneumonia, spinal meningitis, and septicemia (blood poisoning). Children with these problems must be hospitalized and treated with strong antibiotics administered by vein.

**What causes neutropenia?** It is important that doctors know the reason for a child's neutropenia, since the treatment and outcome vary tremendously depending upon the cause. The most serious cause of neutropenia is when production of neutrophils by the bone marrow is decreased because the bone marrow has been damaged or filled up with abnormal cells. This occurs in leukemia (cancer of the blood and bone marrow), aplastic anemia and several other uncommon conditions. These diseases are usually accompanied by changes in other components of the blood such as anemia and a low platelet count. Sometimes a bone marrow test is necessary to exclude the possibility of leukemia.

Neutropenia may also be due to certain drugs, such as the antibiotics Bactrim and Septra and a number of medicines used to treat depression or seizures. In most cases this "allergy" to the drug, resulting in neutropenia, can be easily diagnosed, and if severe treated by stopping the drug.

The most common cause of neutropenia is autoimmune neutropenia or, as it has sometimes been called in the past, chronic benign neutropenia. In this condition, children are "allergic" to their own neutrophils – that is, they make an antibody that attaches to their neutrophils, damages them, and causes them to be destroyed. The bone marrow works "overtime" trying to make more neutrophils, but it can't make enough to keep up with their destruction by the anti-neutrophil antibody. Autoimmune neutropenia is discussed more fully below.

On rare occasions, neutropenia can be congenital (present from birth) and inherited (passed on by genes from one or both parents). Such children are usually documented or suspected as having neutropenia from birth. Sometimes the neutropenia and accompanying infections are extremely severe, whereas in other circumstances they are mild. Occasionally neutropenia can be identified in a parent or other family member. Congenital neutropenia is sometimes difficult to differentiate from autoimmune or chronic benign neutropenia.

The most common form of severe neutropenia from birth is called, appropriately, severe congenital neutropenia (sometimes termed Kostmann syndrome). These children develop chronic inflammation of the gums (which can cause premature loss of teeth) as well as other serious bacterial infections. They usually require G-CSF treatment (see below). A less common form of severe chronic neutropenia is called cyclic neutropenia. Children with this condition have neutrophil counts ranging from zero to near normal varying in a regular or cyclic fashion about every twenty-one days. Often parents can predict when the neutrophil count is lowest because for three or four days during each three week cycle the child experiences fever, mouth sores, and swollen glands. This diagnosis can be made only by checking CBCs two or three times every week for six to eight weeks to confirm the cyclic variability in the ANC.

Finally, neutropenia can rarely be a component of a number of rare and often serious diseases that affect other parts of the body. In these circumstances neutropenia is just one manifestation of the condition. These diseases are often easily differentiated from other forms of neutropenia.

**What are the main features of autoimmune neutropenia?** Autoimmune neutropenia or chronic autoimmune neutropenia of infancy, is the most common cause of chronic neutropenia during childhood. Chronic is arbitrarily defined as lasting more than 8 weeks. Autoimmune neutropenia usually begins at 6 to 12 months of age with frequent ear infections, sore throats, diarrhea, and other minor but troublesome infections. The neutropenia that is identified on the blood count continues for weeks or months. The remainder of the blood count is normal, and overall the child usually appears healthy. There are generally no specific abnormalities on the physical examination. The ANC (see above for definition) is usually between 0 and 500 per cubic millimeter. The neutrophil count fluctuates quite a bit but not in a predictable or cyclic fashion. A blood test for anti-neutrophil antibodies is sometimes positive.

**What causes autoimmune neutropenia?** We really don't know why children with this condition develop the anti-neutrophil antibody – that is, why they become “allergic” to their neutrophils. It does not seem to be associated with a family history of allergic problems or other types of allergies or serious disorders.

**What is the treatment for autoimmune neutropenia?** Since the infections are mild and since the child's bone marrow is able to “push out” enough neutrophils when the need arises, no specific treatment is usually necessary other than prompt initiation of antibiotics whenever the child has a fever. Since fever is a warning sign of infection, whenever fever exists the child should be brought promptly to the pediatrician or family physician for a physical examination, cultures for specific germs, and initiation of antibiotics. Most of the time antibiotics can be given by mouth. However, occasionally children with autoimmune neutropenia may develop pneumonia or other serious infections and will need to be hospitalized. Sometimes the neutrophil count rises temporarily to normal levels during an infection. Some doctors recommend prophylactic antibiotics – i.e., taking an antibiotic every day, even when there is no fever. We generally advise against that however.

Several treatments are available which can temporarily raise the neutrophil count to normal in children with autoimmune neutropenia. However, these treatments are not generally effective for long-term therapy. First, prednisone, a cortisone or steroid- like drug, can suppress the body's allergy and raise the neutrophil count. However, large doses are required and side effects are common. Also, intravenous immune globulin (IVIG), a concentrated form of antibodies derived from blood plasma, can also raise the neutrophil count temporarily. However, IVIG is costly (up to \$3000 for a single dose), requires the child to be connected to an IV for 4 to 6 hours, and works only temporarily. Some children with autoimmune neutropenia whose infections are particularly frequent and troublesome are treated with G-CSF injections (see below).

**What happens to children with autoimmune neutropenia?** Children with autoimmune neutropenia typically have more infections than totally normal children. However, these infections are usually mild and consist of ear, respiratory, and skin infections. Some children have troublesome mouth sores or ulcers similar to fever blisters or canker sores or gum inflammation. Another common (and sometimes serious) site of infection is around

the genital area, especially in little girls. Any redness or swelling in this area or in any other part of the body necessitates seeing a doctor right away. Rarely, the children with autoimmune neutropenia develop life-threatening infections.

Fortunately, children with autoimmune neutropenia usually outgrow their disease. Usually by 3 or 4 years of age the neutrophil count begins to rise and return to normal. There are not enough studies in the medical literature to be certain, but it appears that once the neutrophil count is normal, these children remain well. There is no evidence that they develop other blood disorders or other types of conditions.

**How is severe chronic neutropenia treated?** Most children with severe congenital neutropenia or Kostmann syndrome require treatment with G-CSF (Neupogen), a hormone like substance which is given by subcutaneous (under the skin) injection. Daily treatments are usually required. The medicine is usually effective in raising the neutrophil count (although not always to normal). The result is a healthier life for the child, with fewer infections and improvement in the gingivitis (gum inflammation) and mouth sores which are often problems for these children. G-CSF therapy is usually required indefinitely. The parents are taught how to give the medication, and most children eventually get used to receiving the daily injections. Unfortunately, the medication is very expensive. However, there is a research registry called the Severe Chronic Neutropenia Registry from which free medication can be obtained. Enrollment in the Severe Chronic Neutropenia Registry is part of a long-term research study for which signed consent is required by the parents. In recent years, we have learned that a few children with severe congenital neutropenia, despite G-CSF therapy, may develop a form of leukemia. Therefore, these children need to be regularly monitored.

### **Conclusion**

If you have any questions about neutropenia or about any of the information contained in this brochure, please call one of us in the hematology program at the Center for Cancer and Blood Disorders (214-456-2382).

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