NEUTROPENIA IN BARTH SYNDROME

Barth Syndrome Foundation®

KEY FACTS

- Eight out of every ten individuals with Barth syndrome experience a low blood neutrophil count, called neutropenia, at some stage in their lives
- Almost half of the individuals have "severe chronic neutropenia" where the neutrophil count is intermittently or persistently low long term; such low levels of neutrophils are associated with a potential for serious bacterial infection
- The frequency and severity of neutropenia varies from person to person, even differing between affected members of the same family
- The pattern of neutropenia is unpredictable
- 70% of individuals of those who have Barth syndrome need treatment for neutropenia either occasionally or as a regular therapy

DEFINITION OF NEUTROPENIA

The absolute neutrophil count (ANC) is a measure of the total number of neutrophils present in the blood. Diagnosis is made using a complete blood count (CBC). Average ranges vary depending upon the person's age, racial origin (e.g., lower in some African races), and laboratory standards.

Some laboratories report the absolute neutrophil count (ANC) on a complete blood count (CBC) as either neutrophils or polymorphonuclear cells ("polys" or "PMNs"). In other hospitals, you have to add the counts of "segs" (short for mature, segmented neutrophils) and "bands" (immature neutrophils, with a sausage-shaped nucleus) together to calculate the neutrophil count. Neutrophil counts are generally interpreted as follows:

- **Absolute Neutrophil Count** (ANC)
  - ANC = White Blood Count (WBC) x (% polys or PMNs OR % bands + segs)
- **Normal** ANC: 1500 - 7500/mm^3 (1.5-7.5 x 10^9/L)
  - Infants and toddlers' thresholds for the lower limit of normal are a bit lower 1,000 – 1,200/mm^3 (1.0-1.2 x 10^9/L)
- **Neutropenia**
  - ***Mild***: 1000-1500/mm^3 (1.0-1.5 x 10^9/L)
  - ***Moderate***: 500-1000/mm^3 (0.5-1.0 x 10^9/L)
  - ***Severe***: less than 500/mm^3 (less than 0.5 x 10^9/L)

PATTERNS OF NEUTROPENIA

If neutropenia is found on multiple occasions over a period of months, this is called **chronic neutropenia.**

The neutrophil counts may show a cycling pattern with low points (troughs) occurring every three to four weeks; this is called **cyclical neutropenia**. This is rare in Barth syndrome, and no patient has been shown to cycle consistently.

Most individuals with Barth neutropenia will be neutropenic **intermittently and unpredictably**, which can make neutropenia hard to detect, even in someone who is eventually shown to be severely neutropenic at times.

RISK OF INFECTION

Our body's defenses against bacteria and fungi are weakened during neutropenia, and rapid worsening of infection is much more likely than in someone with a normal neutrophil count. Infections can be very serious and may require antibiotic treatment. The relative risk of infection depends on the depth (severity) of the neutropenia, as follows:

- Normal ANC should be greater than 1500/mm^3 (1.5 x 10^9/L)
    - Infants and toddlers' thresholds for the lower limit of normal are a bit lower 1,000 – 1,200/mm^3 (1.0-1.2 x 10^9/L)
- ANC of 500 to 1000/mm^3 (0.5 to 1.0 x 10^9/L) gives an increased risk for infection
- ANC of 200 to 500/mm^3 (0.2 to 0.5 x 10^9/L) gives a greater risk for severe infection
- ANC lower than 200/mm^3 (0.2 x 10^9/L) gives a **marked risk** of severe infection

HOW TO DETECT SEVERE BARTH NEUTROPENIA

It is crucial to identify anyone with Barth syndrome who is prone to severe neutropenia, although this can be difficult because the disease is so variable. The management of neutropenia in Barth syndrome is a highly specialized area and, if you have not already been offered one, we strongly suggest you ask for a hematology consult. The following are helpful pointers:

1. Approximately one-third of Barth individuals are significantly neutropenic (with ANC less than 1000/mm^3, 1 x 10^9/L) on their very first CBC; half of these will be severely neutropenic (ANC less than 500/mm^3, 0.5 x 10^9/L).
2. Intermittent or frequent severe neutropenia is present long term in at least two-thirds of Barth individuals. Provided that CBCs are not all taken on consecutive days, it is usually detected in the first 10 CBCs performed.
3. Hematologists sometimes recommend a 6-week profile of blood counts on two or three occasions per week to exclude cyclical neutropenia, where neutrophils cycle from low to high and back again over three weeks. However, cyclical neutropenia is rare in Barth syndrome, and such a high frequency of tests can be upsetting for children.
4. If severe neutropenia is not detected during the first admission to the hospital, weekly blood counts for four to six weeks afterward may offer reassurance about the absence of severe neutropenia.
5. An infection can develop during a period of neutropenia, but the neutrophil count then recovers into the normal range by the time of assessment in the hospital, making the causative chronic neutropenia harder to detect.
6. Good times to take CBCs to detect hidden neutropenia; therefore, are at the onset of mouth ulcers or gingivitis, skin spots or severe nappy rash, or when a child is listless or more fatigued for no obvious reason. All of these problems may be caused or aggravated by underlying neutropenia.

INFECTIONS IN BARTH SYNDROME

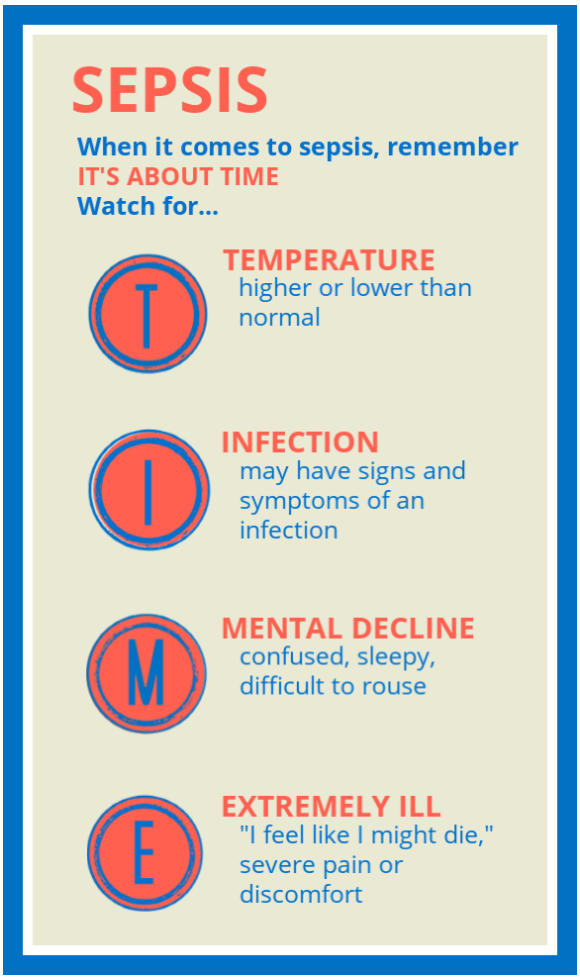
Barth Syndrome Registry[i] data show that one-third of individuals have required admission to hospital on one or more occasions for investigation or treatment of febrile episodes or proven infections. Ear infections occurred in 32%, sinusitis in 18%, and urinary tract infections in 11%. There is also an increased risk of infection associated with foreign bodies, such as peripherally inserted central catheter (PICC) lines and automated implanted cardiac defibrillator (AICD) devices.

In the largest published study of Barth neutropenia (thirty-five patients), the following additional infections occurred:

- Cellulitis (rapidly spreading skin infection, five individuals)
- Pneumonia (lung infection, four)
- Septicemia (blood infection, three; Streptococcus in two, Hemophilus in one)
- Soft tissue abscesses (three)
- Recurrent mouth ulcers (two)
- Gingivitis (gum infection, two)

- Osteomyelitis (bone infection, two)
- Balanitis (foreskin infection, two)
- Septic arthritis (joint infection, one)

Mouth ulcers may be severe and recurrent. They may interfere with eating and even cause visible swelling of the lip or cheek. **Gingivitis** is characterized by inflamed, red gum margins adjacent to the teeth and can cause pain with toothbrushing. Skin problems may include septic spots, boils, and troublesome infections after **insect bites** or **cat scratches**. It is important to look out for spreading skin infection called **cellulitis** anywhere on the skin as this requires urgent antibiotic treatment. This may start from an initial tiny skin break, such as from a bitten nail, cut, scratch, or insect bite. Babies may develop Streptococcal **perianal dermatitis**, seen as bright perianal redness, which may even be accompanied by bleeding or mucus production.



A major concern is that bacterial infections cause fever, increased cardiac output, and metabolic stress. This is a particular challenge for someone with a compromised heart due to Barth syndrome. This explains the desire for early recognition and management of sepsis described in the rest of this fact sheet and for preventive measures in those with severe chronic neutropenia.

THINGS TO REMEMBER

- ❖ Without neutrophils, sepsis from bacterial infections can occur anywhere in your body very quickly.
- ❖ Apply topical antibiotic cream to the site of cuts, scrapes, and burns. `
- ❖ Watch for signs of infection such as redness, warmth to the touch, swelling, and pain with open wounds[ii].
- ❖ Be aware that these common signs of infection may not present when you are neutropenic, even when there is an overwhelming infection.
- ❖ Also, realize that an infection might be internal, so you may not see any visible signs.

WHAT TO DO IF YOU HAVE A FEVER

If you have a temperature higher than 100.4°F (38°C) or have infectious symptoms, your primary doctor or hematologist should be notified.

If you have a temperature of 100.4 to 101.5°F (38 – 38.6°C) for more than 8 hours or a single temperature above 101.5°F (38.6°C), an **immediate examination** by the doctor generally is needed. Health protocols differ from doctor to doctor.

NOTE: Excessively low temperatures can also be a sign of sepsis or impaired heart function. The body is **hypothermic** when the temperature falls below 95°F (35°C). Attempts to warm the peripheral body may result in greater cardiac distress. Your doctor should also be notified if the body temperature becomes low, just as he/she would be for increased body temperature. (Note: It is very important to know what your/your child's normal temperature is, since many individuals with Barth syndrome have a normal temperature that is lower than most people due to their low muscle mass.)

MANAGEMENT OF FEVER

If you need to go to the hospital because of a high fever, you may well be investigated on a "febrile neutropenia protocol." Some or all of the following tests may be ordered:

- CBC with differential and ANC, to look for severe neutropenia
- C-Reactive Protein (CRP, which can help your doctor decide if a bacterial infection is present)
- Blood, urine, and other appropriate cultures
- Urinalysis
- Chest X-ray

Antibiotics may be given on admission to stop rapid worsening of infection. If the CBC shows severe neutropenia, antibiotics may be given for several days. They are then usually stopped if the fever has resolved, and no bacterial infection has been found. If an infection is found, antibiotics will often be given for a longer period. If neutropenia is not present on the CBC the episode may be managed as an outpatient.

Please have a discussion with your doctor about his/her neutropenia protocol, including recommendations for when he/she should be notified. Ask your doctor about 'DIRECT ACCESS'[iii] for neutropenic patients.

Also, please ask them before taking any new prescribed or over-the-counter medications to make sure they don't cause or worsen neutropenia.

LONG-TERM TREATMENT AND CARE (ANTIBIOTICS & G-CSF)

Treatment depends on the severity, symptoms, and/or presence of infection. It also depends on your general health. For example, optimizing general health by treating any nutritional deficiencies is advisable.

It is often impossible to say when someone is severely neutropenic. A daily dose of preventative antibiotics (*e.g.*, cotrimoxazole [Septrin]) is often recommended for those with severe chronic neutropenia as a precautionary measure to protect against infection. Your doctor may also prescribe antibiotics for common infections.

Granulocyte colony stimulating factor (G-CSF) is a drug injected under the skin using a very small needle that stimulates neutrophil production, maturation, and activation from the bone marrow. It may be given every day but has been used successfully over long periods in many Barth syndrome individuals on a three times weekly or alternate daily basis.

- Generic Name: Filgrastim, Lenograstim,
- Trade Names: Neupogen®, Granix®, Granocyte®
- Biosimilars: Zarxio®

Treatment does not always prevent neutropenia but significantly increases the average neutrophil count. Use is described in detail in the medical papers referenced as (1) and (2).

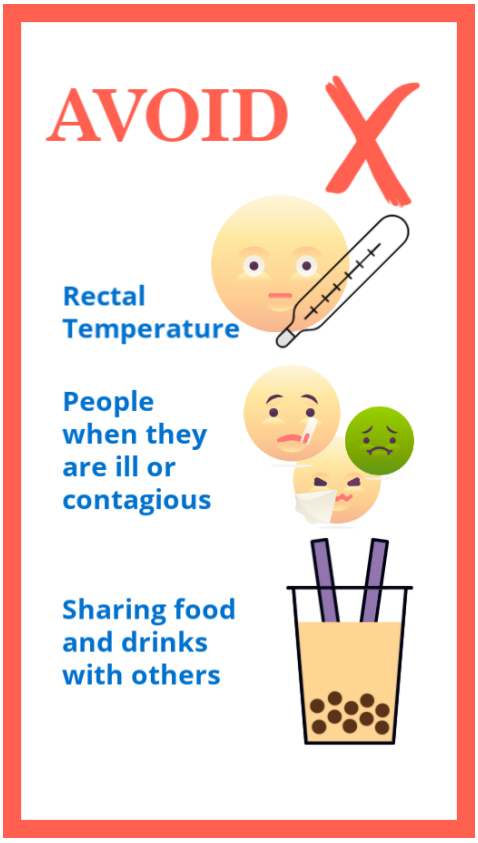
Long-term treatment with granulocyte colony stimulating factor (G-CSF) is frequently recommended for those with severe chronic neutropenia (SCN). This is most important for (a) those with SCN whose counts fall below 200/mm^3 (0.2 x 10^9/L) at any time (due to the severe risk of dangerous bacterial infections at this level), (b) individuals who suffer recurrent mouth ulcers, gingivitis, skin sepsis or bad reactions to insect bites or cat scratches and (c) those who have required previous treatment for severe bacterial infection.

A month-long trial of G-CSF has often been tried in individuals with Barth syndrome SCN, even in the absence of proven bacterial infections, where lethargy, malaise, or failure to thrive are present. The rationale for this is that chronic neutropenia can corrode quality of life (presumably due to occult bacterial infection) in a way that is hard for the individual or their family to appreciate until neutropenia is improved by G-CSF.

VACCINATIONS

In addition to standard immunizations, your doctor will likely suggest that you stay up to date on influenza, pneumococcal and other vaccines[iv].

GENERAL ADVICE



- Educate friends, family, and babysitters about the signs and symptoms, risks and precautions for those who have Barth syndrome
- Maintain good personal hygiene/bathe daily
- Keep your hands clean and avoid placing hands/fingers in your mouth. Keep fingernails short and clean
- Wash raw fruits and vegetables before eating them. They can carry bacteria and fungi
- Care for the mouth before and after meals by brushing with a soft toothbrush
- Wear garden gloves when working in the garden or with flowers and plants

AVOID

- NEVER take rectal temperatures as any break in the skin can lead to an infection
- Do not use enemas or rectal suppositories unless directed by your doctor
- Do not share food, drinks, or food utensils
- Avoid people with colds or spreadable (contagious) diseases (such as chickenpox, colds, herpes zoster, influenza); these are viral infections that can lead to secondary bacterial infections
- Avoid large crowds and traveling when neutropenic
- Avoid construction areas. The dust can release fungus into the air
- Avoid animal droppings. Do not clean litter boxes and birdcages
- Avoid swimming in a small lake or pond if you have any cuts or sores and avoid doing so in any case if the water is stagnant or murky
- Avoid hot tubs/ whirlpools

ADDITIONAL RESOURCES (Click to follow links)

- Absolute Neutrophil Count Calculator
- The Severe Chronic Neutropenia International Registry (SCNIR)
- European Office
- National Neutropenia Network

Physician to Physician Consultation: The Barth Syndrome Foundation and its affiliates maintain a list of multidisciplinary sub-specialists with expertise in the disease who have agreed to speak DIRECTLY with peer physicians during times of crisis. To obtain a list of these physicians, contact The Barth Syndrome Foundation or the regional affiliate lead.

Barth Syndrome Foundation Website: Additional information about Barth syndrome is available for clinicians on the Barth Syndrome Foundation website www.barthsyndrome.org

REFERENCES (click on the title to access or download)

1. **Neutropenia in Barth Syndrome: Characteristics, Risks, and Management**. Steward CG, Groves SJ, Taylor CT, Maisenbacher MK, Versluys B, Newbury-Ecob RA, Ozsahin H, Damin MK, Bowen VM, McCurdy KR, Mackey MC, Bolyard AA, Dale DC. *Curr Opin Hematol*. 2019 Jan;26(1):6-15.

2. **Natural history of Barth syndrome: a national cohort study of 22 patients**. Rigaud C, Lebre AS, Renaud T, Beaupain B, Ottolenghi C, Chabli A, Ansquer H, Ozsahin H, Di Filippo S, De Lonlay P, Borm B, Rivier F, Vaillant MC, Mathieu-Dramard M, Goldenberg A, Viot G, Charron P, Rio M, Bonnet D, Donadieu J. *Orphanet J Rare Dis*. 8, 70 (2013)

3. **The Cellular and Molecular Mechanisms for Neutropenia in Barth Syndrome**. Makaryan V, Kulik W, Vaz FM, Allen C, Dror Y, Dale DC, Aprikyan AA. *Eur J Haematol*. 2012;88:195-209

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[i] Barth Syndrome Registry and Repository 1.0 (BRR 1.0)

[ii] TIME ™ Sepsis Alliance

[iii] An admission straight to the hospital without having to go through the emergency department

[iv] Vaccines, Severe Chronic Neutropenia International Registry (SCNIR)