

Pediatric Neutropenia

Introduction

Neutropenia is a clinically significant entity due to its association with increased risk of infection.

Clinicians tend to differentiate between neutropenia secondary to chemotherapy for the treatment of malignancies and those unrelated to chemotherapy-related bone marrow toxicity. The etiology is diverse in the pediatric population, and ranges from benign causes, such as associated with a viral illness, to inherited conditions, chronic inflammatory diseases, auto-antibody production, and malignancy.

Please note that there is a separate article discussing febrile neutropenia in the pediatric age group.

Definition

Neutropenia is a condition characterized by a depressed neutrophil count. For patients greater than one year of age, it is classified into three stages:

- Mild= an absolute neutrophil count (ANC) 1000-1500 neutrophils/mm³
- Moderate= ANC 500-1000/mm³
- Severe= ANC < 500/mm³

*Where ANC = WBC (cells/mm³) x (%neutrophils + %bands)

In pediatrics, it is important to note that normal values for the ANC vary by age. Furthermore, 3-5% of individuals of African origin have a baseline ANC between 1.0-1.5.⁴

Age	Absolute Neutrophil Count – mean (range) x 10³
Birth	11.0 (6.0-26.0)
12h	15.5 (6.0-28.0)
24h	11.5 (5.0-21.0)
1 week	5.5 (1.5-10.0)
2 weeks	4.5 (1.0-9.5)
1 month	3.8 (1.0-9.8)
6 months	3.8 (1.0-8.5)
1-3 years	3.5 (1.5-8.5)
4 years	3.8 (1.5-8.5)
6 years	4.3 (1.5-8.0)
8 years	4.4 (1.5-8.0)
10-20years	4.4 (1.8-8.0)

Obtained from Segel GB, Halterman JS. "Neutropenia in Pediatric Practice". *Pediatrics in Review*. 2008; 29(1): 12-24

Clinical significance of neutropenia

Neutropenic individuals are at increased risk of infection. The greatest susceptibility of infection is seen with ANC below 500 neutrophils/mm³, prolonged neutropenia below 1000 neutrophils/mm³, and when neutrophil production remains low without recovery. Individuals with neutrophil counts >1000/mm³ are marginally at increased risk of infection when compared to the general population.

Infections secondary to neutropenia commonly involve normal flora colonizing the skin, oropharynx, bronchi, anal canal, and vagina. Gram-negative bacteria, viruses, fungi, and opportunistic pathogens are also common. The most common culprits of serious bacterial infections are of the *Staphylococcus aureus* and gram-negative species.

Symptoms heralding mild to moderate neutropenia include mucosal ulceration, skin infections (abscesses, boils), otitis media, and ultimately serious bacterial infections such as pneumonias, sepsis, and meningitis. Note that even when infection is present, signs may be subtle, as inflammatory processes are largely dependent on adequate numbers and function of neutrophils. Often, a fever remains the sole sign of infection.

Evaluation of the neutropenic patient

As is the case with most presentations in medicine, the cornerstone for evaluating a patient with neutropenia is a thorough history and physical exam. Pertinent elements include:

History: - presence and frequency of infections, in the form of sore throats, oropharyngeal ulcers, fever, otitis, respiratory symptoms, and skin infections (cellulitis, abscesses).

- medication history, including chemotherapeutics, antibiotics, antiepileptics, analgesics, cardiovascular medications, and thiazide diuretics
- toxic ingestions, including alcohol and benzene compounds
- family history of serious infections, neutropenia, hematologic diseases

Physical exam: - oral cavity examination for gingivitis, tooth abscesses, ulcers

- neck, axillae, inguinal, elbow, and popliteal regions for lymphadenopathy
- hepatosplenomegaly

- assess for underlying genetic or syndromic conditions by plotting growth parameters, looking for abnormalities in skin, including pigmentation, hair, and bones.

Once neutropenia is suspected, further investigations are required. The first step is aimed at identifying whether there is isolated neutropenia or associated signs of bone marrow failure, such as thrombocytopenia and anemia. Preliminary steps therefore include a CBC with differential count and smear, to assess neutrophil morphology.

Relevant laboratory investigation in the context of persisting or progressive neutropenia over 2weeks include : - Coombs (direct antiglobulin test) for associated hemolytic anemia

- IgA, IgG, IgM
- antineutrophil antibodies
- viral serologies, including Epstein Barr Virus, cytomegalovirus, respiratory syncytial virus, parvovirus, human immunodeficiency virus
- screening for autoimmune or systemic lupus erythematosus may be appropriate, including antinuclear antibody and anti-double-stranded DNA titers
- nutritional factors may contribute, therefore screen with serum and/or RBC folate, and vitamin B12
- if congenital neutropenia is suspected, DNA analysis for the HAX1 mutation for Kostmann disease and ELA2 mutation for dominant or sporadic severe congenital neutropenia are indicated.
- if neutropenia resolves, but is recurrent, measure ANC three times weekly for six to eight weeks to assess for cyclic neutropenia
- if neutropenia is severe, associated with signs of bone marrow failure (thrombocytopenia, anemia), or prolonged >8weeks, bone marrow aspiration ± culture, cytogenetics are warranted
- if Shwachman Diamond-Oski syndrome is suspected, serum trypsinogen and stool lipids should be obtained.

Etiology

The etiologies of neutropenia in pediatrics are diverse. The most common causes of neutropenia are acquired.

The most frequent cause of transient depression of neutrophil count is a viral illness, notably associated with Epstein-Barr virus, respiratory syncytial virus, influenza A and B, hepatitis, human herpes virus 6 (roseola), varicella, rubella, and rubeola. Other causes of acquired neutropenia, in decreasing frequency of presentation, include medication-induced, primary

autoimmune (5-15 month infants, not associated with recurrent severe infections; despite the presence of granulocyte-specific antibodies, they are able to mobilize neutrophils in the face of infection), secondary autoimmune (e.g.: SLE), chronic idiopathic due to decreased or ineffective production, sequestration in the context of hypersplenism, newborn immune (e.g.: isoimmune neonatal neutropenia due to maternal antineutrophil antibodies), and rarely, nutritionally related.

Inherited causes are less common, but often more severe. They range from benign familial neutropenia to cyclic neutropenia, which lasts for 3-6 days every 21 days, to rare genetic disorders, including:

- Severe congenital neutropenia (SCN) – The normal maturation of neutrophils is stopped at the promyelocyte stage. Presents with severe infections in the first month of life. No spontaneous remissions
- Shwachman Diamond-Oski syndrome – In addition to neutropenia and possibly thrombocytopenia and/or anemia, the patient presents with pancreatic insufficiency, metaphyseal dysostosis (metaphyses of bone are unossified cartilage).

What to tell parents?

Anticipatory guidance is key for families of children with neutropenia. In short, parents must know to bring their children to medical attention should they develop a fever, as febrile neutropenia constitutes a medical emergency (see febrile neutropenia). Education is required regarding prevention of infections, including good oral hygiene, skin care, and the necessity of full immunizations. Finally, potential treatments, including injectable granulocyte stimulating colony factor (G-CSF), should be discussed with families whose children would benefit from the intervention, as well as genetic counseling when appropriate.

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Writer: Gannon Yu

Resident Editor: Katryn Paquette