Neutropenia in Pediatric Practice

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Objectives

After completing this article, readers should be able to:

1. Describe when a patient has true neutropenia, understanding the variation with age and ethnic background.
2. Know the relative risk of infection at various values of the absolute neutrophil count.
3. Discuss the differences between inherited and acquired causes of neutropenia.
4. List the initial studies to evaluate patients who have neutropenia.

Introduction

The significance of neutropenia is a common query to hematology specialists from primary care physicians. Severe neutropenia is defined as an absolute neutrophil count (ANC) of fewer than 500/mcL (0.5×10^9/L) and is a common and expected complication of chemotherapy for childhood neoplasms. This article considers those patients who have neutropenia unrelated to chemotherapy toxicity. This type of neutropenia may be noted when a complete blood count (CBC) is performed in a sick newborn, a febrile child, a child taking chronic medication, or as part of a routine evaluation. Severe hereditary conditions such as Kostmann syndrome and certain immunodeficiency syndromes associated with neutropenia are rare, perhaps 1 per 100,000, and are more likely to present in neonates and infants, although acquired conditions such as immune neutropenia and neutropenia related to infection also occur in this age group. A mild-to-moderate decrease in the ANC (percent neutrophils times the total white count) frequently is seen in viral illness or related to medication use as well as in some healthy persons of African ancestry. A number of inherited conditions associated with neutropenia are associated with other congenital anomalies such as dysplastic thumbs in Fanconi anemia, albinism in Chediak-Higashi syndrome, and dwarfism in the cartilage hair or Shwachman-Diamond syndromes.

When to Order a CBC

A CBC is not ordered routinely for well children examined in the pediatrician's office or when children present with common febrile illnesses such as upper respiratory tract infections or otitis media. A CBC is warranted if clinical findings suggest a more severe bacterial infection. Such clinical findings include, but are not limited to, recurrent infections; prolonged or extreme fever (>103°F [39.5°C]); the spreading of localized bacterial infection; infection of the lung, peritoneum, genitourinary tract, or central nervous system; and suspicion of chronic inflammatory disease, immunodeficiency, or malignancy. A CBC also may be warranted if a patient's clinical course is atypical, prolonged, or complicated by signs and symptoms suggesting the development of a secondary bacterial infection.

Normal Values for the ANC and the Definition of Neutropenia

Normal values for the ANC vary by age, particularly during the first weeks after birth. Normal leukocyte counts and ANCs for children from birth to age 21 years are shown in Table 1. The ANC range is shown for each age, as well. The lower limit of normal is 6,000/mcL (6.0×10^9/L) during the first 24 hours after birth, 5,000/mcL (5.0×10^9/L) for the first week, 1,500/mcL (1.5×10^9/L) during the second week, 1,000/mcL

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Table 1. **Normal Blood Leukocyte Counts***

	Total Leukocytes		Neutrophils			Lymphocytes			Monocytes		Eosinophils	
Age	Mean	(Range)	Mean	(Range)	%	Mean	(Range)	%	Mean	%	Mean	%
Birth	18.1	(9.0 to 30.0)	11.0	(6.0 to 26.0)	61	5.5	(2.0 to 11.0)	31	1.1	6	0.4	2
12 h	22.8	(13.0 to 38.0)	15.5	(6.0 to 28.0)	68	5.5	(2.0 to 11.0)	24	1.2	5	0.5	2
24 h	18.9	(9.4 to 34.0)	11.5	(5.0 to 21.0)	61	5.8	(2.0 to 11.5)	31	1.1	6	0.5	2
1 wk	12.2	(5.0 to 21.0)	5.5	(1.5 to 10.0)	45	5.0	(2.0 to 17.0)	41	1.1	9	0.5	4
2 wk	11.4	(5.0 to 20.0)	4.5	(1.0 to 9.5)	40	5.5	(2.0 to 17.0)	48	1.0	9	0.4	3
1 mo	10.8	(5.0 to 19.5)	3.8	(1.0 to 9.0)	35	6.0	(2.5 to 16.5)	56	0.7	7	0.3	3
6 mo	11.9	(6.0 to 17.5)	3.8	(1.0 to 8.5)	32	7.3	(4.0 to 13.5)	61	0.6	5	0.3	3
1 y	11.4	(6.0 to 17.5)	3.5	(1.5 to 8.5)	31	7.0	(4.0 to 10.5)	61	0.6	5	0.3	3
2 y	10.6	(6.0 to 17.0)	3.5	(1.5 to 8.5)	33	6.3	(3.0 to 9.5)	59	0.5	5	0.3	3
4 y	9.1	(5.5 to 15.5)	3.8	(1.5 to 8.5)	42	4.5	(2.0 to 8.0)	50	0.5	5	0.3	3
6 y	8.5	(5.0 to 14.5)	4.3	(1.5 to 8.0)	51	3.5	(1.5 to 7.0)	42	0.4	5	0.2	3
8 y	8.3	(4.5 to 13.5)	4.4	(1.5 to 8.0)	53	3.3	(1.5 to 6.8)	39	0.4	4	0.2	2
10 y	8.1	(4.5 to 13.5)	4.4	(1.8 to 8.0)	54	3.1	(1.5 to 6.5)	38	0.4	4	0.2	2
16 y	7.8	(4.5 to 13.0)	4.4	(1.8 to 8.0)	57	2.8	(1.2 to 5.2)	35	0.4	5	0.2	3
21 y	7.4	(4.5 to 11.0)	4.4	(1.8 to 7.7)	59	2.5	(1.0 to 4.8)	34	0.3	4	0.2	3

*Numbers of leukocytes are in thousands/mcL ($\times 10^9$/L), ranges are estimates of 95% confidence limits, and percentages refer to differential counts. Neutrophils include band cells at all ages and a small number of metamyelocytes and myelocytes in the first few postnatal days.
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(1.0×10^9/L) between 2 weeks and 1 year of age, 1,500/mcL (1.5×10^9/L) from ages 1 year through 10 years, and 1,800/mcL (1.8×10^9/L) thereafter. However, most reports use 1,500/mcL (1.5×10^9/L) as the lower limit of normal for white adults. Adults and children of African extraction may have ANCs between 1,000 and 1,500/mcL (1.0 and 1.5×10^9/L), which overlaps the values observed in patients who have "mild neutropenia." We estimate from the data available that at least 3% to 5% of persons of African ancestry have ANCs below 1,500/mcL ($1/5\times10^9$/L).

Risk Assessment

For patients older than 1 year of age, mild neutropenia is defined as an ANC of 1,000 to 1,500/mcL (1.0 to 1.5×10^9/L), moderate neutropenia as an ANC of 500 to 1,000/mcL (0.5 to 1.0×10^9/L), and severe neutropenia as an ANC of less than 500/mcL (0.5×10^9/L). Usually, patients are highly susceptible to bacterial infection if the ANC is less than 500/mcL (0.5×10^9/L), with the risk of infection greatest at the lowest ANCs. Increased infection risk also is related to longer durations of neutropenia and is highest if the neutrophil count remains low without recovery. If neutrophils can be mobilized to respond, infection is less likely to occur, as can be seen in immune neutropenia, a condition in which there is myeloid hyperplasia and heightened neutrophil production. Although serious bacterial infections are observed when the ANC is between 500 and 1,000/mcL (0.5 and 1.0×10^9/L), they are much less frequent or severe. There is little or no heightened infectious risk if the ANC is greater than 1,000/mcL (1.0×10^9/L).

Pyogenic Infections Associated With Neutropenia

Moderate-to-severe neutropenia may portend an inadequate neutrophil response to bacterial infection. The clinical signs of neutropenia may include ulcerations of the oral mucosa or gingival inflammation. Otitis media, skin infections that include cellulitis and pustules, adenitis, pneumonia, and bacterial sepsis may occur. The source of the infection may be the child's own skin or bowel flora. Perianal infection and ischiorectal fossa abscesses sometimes are seen. The most common offending organisms are *Staphylococcus aureus* and the gram-negative bacteria (see section on fever and neutropenia).

Initial Evaluation of the Patient Who Has Neutropenia

The initial evaluation (Table 2) should include a history and physical examination. It is critical to know whether the child has had recurrent bacterial infections, whether there is a family history of neutropenia or infection, and after physical examination, whether there are any associated congenital anomalies that suggest an inherited syn-

Table 2. Initial Evaluation for Patients Who Have Neutropenia

History

- History of underlying disease, congenital anomalies, medication exposure, or recent infection or mouth ulceration
- Other family members who have neutropenia and serious infections, hospitalizations, or blood diseases

Physical Examination

- Short stature, malnutrition, skeletal abnormalities
- Abnormal skin pigmentation, dystrophic nails, leukoplakia, warts, albinism, fine hair, eczema, skin infections, adenopathy, and organomegaly

CBC With Differential Count and Reticulocyte Percentage

- Confirm the finding of neutropenia, evaluate neutrophil morphology, and assess whether red cell production is increased or decreased
- If the neutropenia resolves and is recurrent, repeat two to three times per week for 6 weeks

Other Laboratory Tests

- Blood smear
- Coombs test (direct antiglobulin test) for associated hemolytic anemia
- Immunoglobulins (IgA, IgG, IgM)
- Serology (Epstein–Barr virus, cytomegalovirus, respiratory syncytial virus, parvovirus, etc, as indicated clinically)
- Antineutrophil antibodies

drome. Mouth ulcers may occur in association with neutropenia, and the presence of gingivitis is a good indicator that the patient cannot mobilize adequate neutrophils and, thus, may be susceptible to severe infection. If neutropenia is suspected, it is important to determine if the patient has isolated neutropenia or neutropenia associated with anemia or thrombocytopenia. The clinical implication of deficits of more than one cell type is different from that of an isolated neutropenia. Anemia or thrombocytopenia in conjunction with neutropenia often reflects a more generalized marrow failure syndrome such as aplastic anemia or a marrow infiltrative process such as leukemia. The neutropenia must be confirmed by repeating the CBC to avoid an extensive evaluation due to a laboratory error.

It is reasonable to observe the patient who has a viral illness and mild-to-moderate neutropenia and otherwise appears well. If the neutropenia persists or progresses after 1 to 2 weeks, additional evaluation is necessary. If the neutropenia is recurrent, obtaining blood counts two to three times per week for several weeks can establish any cycles of neutropenia. If additional evaluation is warranted, the presence of antineutrophil antibodies suggests immune neutropenia, and quantifying immunoglobulins, including IgG, IgA, and IgM, and the distribution of lymphocyte subsets may indicate an underlying immunodeficiency syndrome. In addition, screening tests for systemic lupus erythematosus, including an antinuclear antibody titer and anti-double-stranded DNA, can be helpful. If a patient has severe neutropenia, referral to a hematologist is necessary. If severe congenital neutropenia is suspected, assessing for the *HAX1* mutation for Kostmann disease and *ELA2* mutation for dominant or sporadic severe congenital neutropenia is indicated. A detailed presentation of the potential laboratory evaluation by hematology is shown in Table 3.

Acquired Neutropenia

Infection

When evaluating the child who has neutropenia, the acquired neutropenias are considered first because of their greater frequency (Table 4). The most common underlying cause for mild-to-moderate neutropenia is transient marrow suppression due to a variety of viral infections. Neutropenia is seen in patients who have Epstein-Barr virus, respiratory syncytial virus, influenza A and B, hepatitis, and human herpesvirus 6 infections as well as the exanthems (to which most children are immunized), including varicella, rubella, and rubeola. Neutropenia occurs often during the first few days of the viral illness and persists for 3 to 8 days. Severe bacterial infection also may cause neutropenia rather than neutrophilia, which can be transient if the bacterial infection is treated effectively. Other bacterial or rickettsial diseases such as typhoid fever, tuberculosis, and Rocky Mountain spotted fever may cause neutropenia.

Drug-induced

A variety of medications (Table 5), including antibiotics, anticonvulsants, and anti-inflammatory agents, have been associated with neutropenia, a frequent reason for referral to hematology. The dilemma is how to treat the patient who requires the particular medication that is causing a potentially dangerous adverse effect. If the drug-induced neutropenia is idiosyncratic, its severity and persistence may be impossible to predict, and it is difficult to avoid discontinuing the drug. A similar situ-

Table 3. **Detailed Laboratory Evaluation of Neutropenia**

Test	Findings
CBC and Differential Count	ANC less than lower limit for age (Table 1) ± anemia and thrombocytopenia
Reticulocyte % (Index)	Increased if RBC destruction, as in Evans syndrome (or bleeding) Decreased in marrow failure syndromes
Blood Smear	Confirms decreased ANC Morphologic abnormalities of neutrophils, as in Chediak-Higashi syndrome Associated RBC or platelet findings
Coombs Test (Direct Antiglobulin Test)	Detects antibodies to RBC, as in Evans syndrome or systemic lupus erythematosus
ANA Anti-double-stranded DNA	Screen for systemic lupus erythematosus
Antineutrophil Antibody	May be found in alloimmune or autoimmune neutropenia
IgG, IgA, IgM	Screen for underlying immunodeficiency IgG and IgA may be decreased and IgM elevated
Lymphocyte Subtypes	Decreased T, B, or NK cells in underlying immunodeficiency
Marrow Examination	May show no maturation beyond the promyelocyte stage in severe congenital neutropenia; myeloid hyperplasia with few or no bands or mature neutrophils in immune neutropenia Cytogenetics may reveal a neoplastic clone, as in leukemia
DNA Analysis (*HAX1, ELA2, Gfil) (FANC, DKC, RPS19*)	Specific for genetic diagnosis—see Table 6 for specific genes
Serum Trypsinogen, Other Stool Fat	Low serum trypsinogen and elevated stool fat found in Shwachman-Diamond syndrome
Nutritional	Serum vitamin B_{12}, RBC, and serum folic acid

ANA=antinuclear antibody, ANC=absolute neutrophil count, CBC=complete blood count, RBC=red blood cell.

ation exists for drug-induced immune neutropenia. If the drug acts as a hapten, leading to production of an antibody, the ANC should improve within 1 to 2 weeks after cessation of drug administration. On the other hand, if the neutropenia is mild, it may be dose-related, and drug administration could be titrated to permit continued use.

Immune

Neonatal alloimmune neutropenia results from the transfer of fetal cells to the maternal circulation, causing the mother to produce antibody to fetal antigens not present on her own cells in a manner similar to Rh disease. A variety of neutrophil-specific antigens have been identified and are designated HNA-1a (NA1), HNA-1b (NA2), HNA-2a (NB1), HNA-3a (5b), HNA-4a (MART), and HNA-5a (OND). Because the half-life of IgG is approximately 5 to 6 weeks, alloimmune neutropenia usually disappears after age 2 to 3 months. If infections are associated with the neutropenia, granulocyte colony-stimulating factor (G-CSF) may be used to stimulate a heightened neutrophil count.

Passive transfer of maternal antibody also may cause neonatal neutropenia. Pregnant women who have either primary immune neutropenia or immune neutropenia due to a disease such as lupus may transfer IgG antineutrophil antibodies passively to the developing fetus. This type of neonatal neutropenia also is transient.

Primary autoimmune neutropenia of infancy and childhood may be the cause of chronic neutropenia. The diagnosis may be established in most patients with the demonstration of antineutrophil antibodies by leukoagglutination or immunofluorescence. These antibodies may develop as a result of "molecular mimicry," wherein an epitope on the surface of an infecting virus stimulates production of an antibody that then cross-reacts with a similar antigen on the surface of the neutrophil, leading to neutrophil destruction. Such antibodies often are directed against NA1. Marrow examination reveals myeloid hyperplasia but with few mature neutrophils (pictures of normal bone marrow and marrow in immune neutropenia are available in the online edition of this issue of *Pediatrics in Review* [http://pedsinreview.aappublications.org/cgi/content/full/29/1/12/DC2]). The neutropenia may be profound, and the child may develop ear, pulmonary, skin, or other infections. Such infections are treated primarily with antibiotics. However, glucocorticoids such as prednisone may suppress the immune destruction of neutrophils, and more recently, G-CSF has been used to heighten neutrophil production to overcome the antibody-induced destruction. The initial

Table 4. **Acquired Neutropenia**

Condition	Pathogenesis	Occurrence	Associated Findings
Infection	Viral marrow suppression or viral-induced immune neutropenia	Common	EBV/parvovirus/HHV6 and other viruses
	Bacterial sepsis-endotoxin suppression	Less common	Severe infection
Drug-induced	Direct marrow suppression	Common	Underlying condition
	Immune destruction	Less common	
Autoimmune	Primary (molecular mimicry)	Common	Monocytosis common
	Secondary (SLE, Evans syndrome)		
Newborn Immune	Alloimmune—maternal sensitization	Rare	Antigen difference in newborn and mother
	Due to maternal autoimmune neutropenia		Maternal neutropenia
Chronic Idiopathic	Ineffective or decreased production	Common	Consider also familial benign neutropenia
			Often asymptomatic
Sequestration	Hypersplenism	Common if spleen is enlarged	Mild neutropenia
			Enlarged spleen—many causes
Nutritional	Vitamin B_{12} or folic acid deficiency	Rare in children	Marrow megaloblastic
	Impaired DNA processing		Hypersegmented neutrophils

EBV=Epstein-Barr virus, HHV=human herpesvirus, SLE=systemic lupus erythematosus.

dose of prednisone usually is 2 mg/kg per day administered orally in two divided doses, and the initial dose of G-CSF is 5 mcg/kg administered subcutaneously once a day. These therapies usually are administered under the guidance of a pediatric hematologist.

Secondary autoimmune neutropenia more often affects adults and is seen in systemic autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis (Felty syndrome), or systemic sclerosis; in certain infections, such as those due to human immunodeficiency virus, parvovirus B19, or *Helicobacter pylori;* or in drug-induced neutropenia. Secondary autoimmune neutropenia also has been reported in association with Wilms tumor and Hodgkin disease. Treatment of secondary neutropenias is directed toward the primary disease. Administration of G-CSF may be considered if the neutropenia is severe and protracted.

Chronic Idiopathic

Chronic idiopathic neutropenia likely represents a variety of disorders and is not well characterized. Some of the patients classified as having chronic idiopathic neutropenia actually may have immune neutropenia or familial benign neutropenia. The "idiopathic" diagnosis may be considered when other known causes have been eliminated. The clinical severity appears to be related to the severity of neutropenia, and the marrow findings are not consistent. Ineffective or decreased production of neutrophils may be seen in this condition. Many hematologists watch patients whose conditions appear truly "idiopathic" and whose neutropenia is mild and not associated with an increase in infections, keeping the evaluation to a minimum rather than pursuing a more extensive evaluation that often yields nothing. When therapy is indicated, glucocorticoids and G-CSF have been used.

Sequestration

Splenomegaly and hypersplenism from any cause may result in mild neutropenia (1,000 to 1,500/mcL [1.0 to 1.5×10^9/L]) due to sequestration. Enlarged spleens may be present in patients who have chronic hemolytic anemias, liver disease, or portal hypertension and in metabolic disorders such as Gaucher disease. These conditions also may result in anemia and thrombocytopenia. Results of the marrow examination are normal or show mild hyperplasia of all elements. Usually, this problem does not require treatment unless the cytopenias are profound or management of the underlying condition requires treatment. In some cases, splenectomy is necessary.

Table 5. **Partial List of Drugs Associated With Idiosyncratic Neutropenia**

Drug	Possible Mechanism		
	Direct Suppression	Metabolite Suppression	Immune Destruction
Analgesics/Anti-inflammatory Agents			
Aminopyrine			X
Ibuprofen			X
Indomethacin	X		
Phenylbutazone	X		
Antibiotics			
Chloramphenicol	X		
Penicillins	X		X
Sulfonamides	X		
Anticonvulsants			
Phenytoin			X
Carbamazepine		X	
Antithyroid Agents			
Propylthiouracil			X
Cardiovascular Agents			
Hydralazine			X
Procainamide			X
Quinidine			X
Hypoglycemic Agents			
Chlorpropamide			X
Tranquilizers			
Chlorpromazine	X		
Phenothiazines	X		
Other			
Cimetidine, ranitidine	X		
Levamisole			X

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Nutritional Deficiency

Both vitamin B_{12} and folic acid deficiency may result in ineffective hematopoiesis with megaloblastic erythropoiesis. Patients who develop megaloblastic anemia generally are adults. In addition to megaloblastic anemia, the impairment in DNA processing may result in neutropenia. Neutrophil nuclear maturation is impaired, leading to hypersegmentation of the neutrophil nuclei in the blood as well as ineffective marrow proliferation and maturation. Treatment involves replacement of the deficient factor.

Inherited Neutropenia (Table 6)

Severe Congenital

Severe congenital neutropenia may present as early as infancy with umbilical infection, pyoderma, oral ulcers, pulmonary infections, or perineal infections of the labia or perirectal area. The ANC is less than 500/mcL (0.5×10^9/L) and often less than 200/mcL (0.2×10^9/L). Severe congenital neutropenia may be inherited as an autosomal recessive condition (Kostmann syndrome) involving mutations in the *HAX1* gene that is involved in signal transduction. It also may be inherited as an autosomal dominant condition, with mutations in the neutrophil elastase gene (*ELA2*) or, more rarely, in the *GFI1* gene that targets *ELA2*. It has been suggested that such gene mutations result in accelerated apoptosis of myeloid precursors. Examination of the marrow reveals an arrest at the promyelocyte stage of development (a picture of bone marrow in severe congenital neutropenia is available in the online edition of this issue of *Pediatrics in Review* [www.pedsinreview.org]). Few or no myelocytes, metamyelocytes, bands, or mature neutrophils are seen, and there may be an associated monocytosis and eosinophilia in the blood. Affected patients have a very high risk of developing a myelodysplastic syndrome or acute myelogenous leukemia, a consequence that has become more evident as patients live longer with treatment using G-CSF. Table 7 describes G-CSF administration.

Table 6. Inherited Neutropenia

Condition	Inheritance	Pathogenesis	Occurrence	Associated Findings
Severe Congenital (Kostmann)	AR	*HAX1* mutations causing disturbed regulation of myeloid homeostasis Marrow arrest at the promyelocyte stage	Rare (1/1 to 200,000)	ANC <500/mcL (0.5×10^9/L) Leukemia risk of 15% to 20%
Severe Congenital	AD and sporadic	*ELA2* mutations on the face of the molecule opposite the active site causing accelerated apoptosis	Rare (1/1 to 200,000)	ANC <500/mcL (0.5×10^9/L) Leukemia risk of 5% to10%
		GFI1 mutations target *ELA2*	Two families	↓ T and B cells Marrow has immature myeloid cells
Cyclic	AD	*ELA2* mutations clustering near the active site of the molecule	0.5 to $1/10^6$	21-day cycle with fever and mouth ulcers
Shwachman-Diamond Syndrome	AR	*SDS* gene conversion from the pseudogene, resulting in failure of neutrophil production Defect in RNA processing Decreased CD34 cells	1/50,000	Pancreatic exocrine insufficiency, short stature, metaphyseal dysplasia, marrow failure, and leukemia risk (15%)
Familial Benign	AD	Decreased marrow release	Common	Africans and Yemenite Jews Periodontal disease
Marrow Failure Syndromes:				
Fanconi	AR	Gene (*FANC*) defects in DNA repair	$1/10^6$	Dysplastic thumbs, pancytopenia, other anomalies
Dyskeratosis Congenita	Usually XR (also AR and AD)	*DKC1* (*TERC or TERT* in AD) mutations Telomerase defect, ribosomal dysfunction		Abnormal skin pigmentation, leukoplakia, dystrophic nails
Blackfan Diamond Syndrome	Sporadic 75% AR and AD	*RPS19* mutations that affect a ribosomal protein in 25% of families ? Mechanism of erythropoietic failure Many patients respond to glucocorticoids		Erythroid failure syndrome Neutropenia in 25% to 40% Thumb and craniofacial anomalies Increased RBC adenosine deaminase Leukemia risk of 2% to 3%
Dysgammaglobulinemia or Hyper-IgM	XR (also AR)	CD40 ligand mutations ? Immune neutropenia, but antineutrophil antibody is negative		↓ IgG, ↓ IgA, ↑ IgM May have immune thrombocytopenia and anemia Neutropenia only seen in XR
WHIM Syndrome and Myelokathexis	AD (also ?AR)	Imbalance in pro- and anti-apoptosis Defect in CXCR4 receptor leading to failure of neutrophils to leave the marrow	Case reports	Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM)

Table 6. **Inherited Neutropenia Continued**

Condition	Inheritance	Pathogenesis	Occurrence	Associated Findings
Chediak-Higashi Syndrome	AR	CHS1 ?defect in lysosomal fission Abnormal protein trafficking Decreased neutrophil chemotaxis, degranulation, and killing	Rare	↓ NK and T-cell function Albinism Neurologic damage and giant lysosomes
Reticular Dysgenesis	AR	Stem cell failure in lymphoid and myeloid development	Rare	Severe combined immunodeficiency with neutropenia
Cartilage Hair	AR	*RMRP* mutations Defect in a ribonuclear protein ribonuclease	Rare	Fine hair, short-limbed, dwarfism, lymphopenia, ↓ CD4 and ↓ CD8 cells Infections, particularly varicella zoster
Metabolic Glycogen Storage Disease 1b (also aminoacidopathies)	AR	*G6PT1* mutations (glucose-6-phosphate translocase) in 1b	$1/10^5$ live births	Hypoglycemia, dyslipidemia, ↑ uric acid, ↑ lactic acid, and neutropenia in most patients
Griscelli Syndrome Type 2	AR	*RAB27A* mutations Impaired lytic granule release	Rare	Partial albinism, neutropenia, infections, and thrombocytopenia with hemophagocytosis and T-cell defect
Barth Syndrome	XR	*TAZ* mutation on the X chromosome Cardiolipin defect	Rare	Dilated cardiomyopathy Skeletal myopathy Mitochondrial abnormalities
Wiscott-Aldrich Syndrome	XR	Mutations in the Cdc42 binding site in the *WASP* gene Results in X-linked neutropenia	1 to $10/10^6$	Impaired lymphoid development and maturation of monocytes Associated with eczema, thrombocytopenia, and immune deficiency
Selective IgA Deficiency	Unknown or multifactorial	Unknown	Common (1/600)	Infections of the upper and lower respiratory tracts in one third of patients

AR=autosomal recessive, AD=autosomal dominant, ANC=absolute neutrophil count, Ig=immunoglobulin, NK=natural killer, RBC=red blood cell, XR=X-linked recessive.

Cyclic

Cyclic neutropenia is characterized by approximately 21-day cycles of changing neutrophil counts, with neutropenia spanning 3 to 6 days. The nadir of the neutrophil count may be in the severe range. Fever and oral ulcerations usually are seen during the nadir. Patients also may develop gingivitis, pharyngitis, and skin infections. However, by the time the patient comes to medical attention, the neutrophil count may be recovering. Therefore, diagnosing cyclic neutropenia may require obtaining blood counts two to three times per week for 4 to 6 weeks in an effort to observe the periodicity of the cycle.

More serious infections include pneumonia, necrotizing enterocolitis with peritonitis, and *Escherichia coli* or *Clostridium* sepsis. Marrow findings reflect the state of neutropenia. Prior to the ANC nadir, the marrow may resemble that associated with severe congenital neutropenia before proceeding to a recovery phase. The periodicity of marrow activity also may be seen in the erythroid series. As in severe congenital neutropenia, mutations occur in the *ELA2* gene, but at different locations (Table 6). Also, there does not appear to be an increased risk of myelodysplasia or acute myelogenous leukemia. Prophylactic G-CSF has been recommended to prevent severe symptoms at the nadir of the cycle.

Table 7. **Treatment of Neutropenia**

Granulocyte Colony-stimulating Factor	Initially 5 mcg/kg per day subcutaneously If no response after 1 wk, the dose may be doubled repeatedly up to 100 mcg/kg per day
Glucocorticoids	Prednisone 2 mg/kg per day PO for immune neutropenia
Nutritional	Vitamin B_{12} 1,000 mcg each week for 5 to 6 wk, then q 1 mo subcutaneously if B_{12}-deficient Folic acid 1 mg/d PO
Splenectomy	Prior immunization to encapsulated bacterial (pneumococcus, *Haemophilus influenzae* type b, meningococcus) required Prophylactic penicillin after splenectomy 125 mg bid <age 5 y; 250 mg bid ≥age 5 y
Medication Revision	If possible, reduce dosage or discontinue any medications associated with neutropenia
Antibiotics	As appropriate for patient's age, type and location of infection, and if possible, culture results
Granulocyte Transfusion	May be useful in invasive bacterial or fungal infections for patients who have severe neutropenia (ANC <500/mcL [0.5×10^9/L]) who are not responding to antibiotics

Shwachman-Diamond Syndrome

Patients who have Shwachman-Diamond syndrome usually have a mild-to-moderate degree of neutropenia in association with exocrine pancreatic insufficiency, short stature, metaphyseal dysplasia, marrow failure, and the risk of myelodysplasia and acute myelogenous leukemia. A defect in RNA processing leads to a failure of neutrophil development. Malabsorption and failure to thrive are common problems, and affected patients may develop infections because of the neutropenia and a possible defect in chemotaxis. G-CSF has been used when the neutropenia is symptomatic; pancreatic replacement therapy is required.

Marrow Failure Syndromes

FANCONI ANEMIA. Fanconi anemia is characterized by pancytopenia (with all cell lines affected). It presents most commonly in the second half of the first decade of life, and thrombocytopenia may precede the development of anemia and neutropenia. The marrow is hypoplastic and resembles aplastic anemia. The disease is characterized by a defect in DNA repair leading to extensive chromosomal breakage, and there is hypersensitivity to DNA cross-linking agents such as diepoxybutane in vitro. Affected patients have mutations in the *FANC* genes, primarily in *FANC A*, *C*, and *G*. Clinically, patients may have short stature; dysplastic thumbs; or heart, kidney, or eye abnormalities. They have a nearly 10% risk of developing a myelodysplastic syndrome or acute myelogenous leukemia. The pancytopenia may respond to androgen treatment, which is particularly difficult to use in young women. G-CSF and other cytokines may be effective, but their efficacy may not be sustained. The only curative treatment for Fanconi anemia is stem cell transplantation.

DYSKERATOSIS CONGENITA (ZINSSER-ENGMAN-COLE SYNDROME). This abnormality results from a mutation in the *DKC1* gene that encodes dyskerin, a component of the telomerase complex, which is responsible for the elongation of DNA. Affected patients exhibit abnormal skin pigmentation, leukoplakia, and dystrophic nails. The skin and mucosal lesions appear in the second decade, and marrow failure develops in early adulthood. Patients may present with isolated neutropenia, but more often, all cell lines are affected. Hematopoietic growth factors, such as G-CSF, may be useful in treating the neutropenia. Abnormalities of T-helper cells and dysgammaglobulinemia may contribute to a susceptibility to infection in some patients.

Syndromes Associated With Neutropenia and Immunodeficiency

A variety of syndromes include neutropenia and abnormalities in T, B, or natural killer cell function. The combined problem of neutropenia and immunodeficiency makes patients who have these syndromes more susceptible to infectious complications. One condition is the hyper-IgM syndrome, in which concentrations of IgG and IgA are diminished and IgM is heightened. The nature of the neutropenia is not known, but may be immune in origin, although antineutrophil antibodies are negative. Other syndromes associated with neutropenia and immunodeficiency are listed in Table 6; their associated findings are particularly important for defining these rare syndromes.

Fever and Neutropenia

A very difficult issue is how best to treat a patient who has fever and neutropenia. Although detailed guidelines have

Table 8. **Fever and Neutropenia**

ANC	Etiology of Fever	Management	Outpatient/Hospital
1,000 to 1,500/mcL	Viral (frequent)	Supportive	Outpatient
(1.0 to 1.5×10^9/L) Mild	Bacterial: URI (sinusitis, purulent rhinitis), otitis media, local skin infections	Indicated PO antibiotics	Outpatient
	Bacterial pneumonia, systemic symptoms, GU infections, lymphadenitis	Blood cultures Specific cultures Best estimate antibiotics Observation for progression	Outpatient unless progression
500 to 1,000/mcL	Viral	Supportive	Outpatient
(0.5 to 1.0×10^9/L) Moderate	Bacterial: URI (sinusitis, purulent rhinitis), otitis media, local skin infections	Blood and other cultures Indicated PO or IV antibiotics	Outpatient/Hospital*
	Bacterial pneumonia, systemic symptoms, GU infections, lymphadenitis	Blood cultures Specific cultures Sepsis evaluation Parenteral broad-spectrum antibiotics	Hospital
<500/mcL (0.5×10^9/L) Severe	Assume bacterial	Blood cultures Specific cultures Sepsis evaluation Parenteral broad-spectrum antibiotics	Hospital

ANC=absolute neutrophil count, GU=genitourinary, IV=intravenous, PO=oral, URI=upper respiratory tract infection.
*Either outpatient or hospital care may be appropriate for children who have moderate neutropenia and local infection, depending on the patient's underlying disorder and the anticipated time for recovery of the ANC. Children who have congenital/chronic neutropenia likely would benefit from treatment in the hospital because recovery of the ANC is less likely without cytokine treatment. In contrast, neutropenia due to viral suppression, antibody effect, or some medication exposures may allow a better response to localized bacterial infection and be managed on an outpatient basis.

been formulated for patients who have chemotherapy-induced neutropenia, relatively few data are available for patients who have neutropenia not associated with cancer treatment. Fever is defined as a temperature greater than 101°F (38.3°C) or a temperature of at least 100.4°F (38°C) for longer than 1 hour. Most authors categorize the severity of neutropenia into three groups (Table 8). The decision surrounding treatment and potential hospitalization depends on the likelihood of bacterial infection, the location and severity of the infection, the severity of the neutropenia, and the likelihood and timeframe of neutrophil recovery. Furthermore, the age of the patient, the proximity of specialized medical care, and the reliability of the guardians should be considered in the management decision. Table 8 presents a starting point for consideration of "what to do" and is based on the principles used in the care of neutropenic chemotherapy patients and the concerns of pediatric hematologists and infectious disease specialists.

Specific recommendations for initial broad-spectrum antibiotic coverage depend on the prevalence of organisms in each community and hospital and their susceptibility patterns. Approximately two thirds of isolated organisms are gram-positive (Table 9). Initial antibiotic treatment may employ a single broad-spectrum antibiotic such as ceftazidime or cefepime. Alternatively, an aminoglycoside can be combined with a beta-lactam drug such as a third- or fourth-generation cephalosporin for broad antibiotic coverage. The initial addition of vancomycin is controversial, but should be done if resistant organisms are suspected because of their prevalence in the community.

When to discontinue antibiotic treatment is a particular problem for physicians caring for patients who have

Table 9. Bacterial Causes of Febrile Episodes in Neutropenic Patients

Aerobic Bacteria (~90%)*
Gram-positive Cocci (~45%)
Staphylococcus
Coagulase-positive (*S aureus*)
Coagulase-negative (*S epidermidis* and others)
Streptococcus
S pneumoniae
S pyrogenes
viridans group
Enterococcus faecalis/faecium
Gram-positive bacilli (rare)
Corynebacterium sp
Gram-negative Bacilli (~45%)
Escherichia coli
Klebsiella sp
Pseudomonas aeruginosa
Anaerobic Bacteria (4% to 5%) (Often Polymicrobial)
Gram-positive Cocci (normal mouth flora)
Peptococci
Peptostreptococci
Gram-negative Bacilli
Bacteroides fragilis
Fusobacterium sp

*Percentages observed in patients receiving chemotherapy who were immunocompromised (Mathur P, Chaudry R, Kumar L, Kapil A, Dhawan B. A study of bacteremia in febrile neutropenic patients at a tertiary-care hospital with special reference to anaerobes. *Med Oncol.* 2002;19:267–272). Specific organisms were reported by Hughes WT, Armstrong D, Bodey GP, et al. 1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. Infectious Diseases Society of America. *Clin Infect Dis.* 1997;25:551–573 and Merck & Co, Inc, Whitehouse Station, NJ, USA: 1995–2007 (http://www.merck.com/mmpe/sec14/ch178/ch178j.html).

neutropenia. If the blood cultures are negative and the child becomes afebrile, antibiotics can be stopped, even if the neutropenia persists. Usually, antibiotics are continued if the cultures are negative and the child remains febrile and neutropenic. Fever generally resolves quickly with antibiotic therapy if the neutropenia resolves. If the cultures are positive and the child is no longer febrile and neutropenic, the prescribed antibiotic treatment may be completed with oral antibiotics at home. If the cultures are positive and the child is afebrile but persistently neutropenic, the course of antibiotics usually is completed in the hospital. The child then is observed for 24 to 48 hours prior to discharge. The persistence of neutropenia requires the additional evaluation described in this article and consideration of treatment with G-CSF if the neutropenia is profound and there are frequent infections.

The Medical Emergency of Fever With Severe Neutropenia

Hospitalization is required for patients who have severe neutropenia (specifically neutrophil counts less than 500/mcL [0.5×10^9/L]), moderate neutropenia and severe infection, or any level of neutropenia combined with ill appearance, as well as consultation with pediatric hematology and pediatric infectious disease services. Patients who have immune neutropenia of infancy often can be treated as outpatients because they can mobilize neutrophils transiently. The hematologist can help establish the cause of the neutropenia, and the infectious disease specialist can help identify the type and susceptibility of the infecting bacteria in the specific community. If the patient is seen in the office, a blood culture (aerobic and anaerobic) and a urinalysis and urine culture (no catheter should be used) can be obtained and the initial dose of antibiotics administered. If possible, an intravenous line should be kept open. The patient should be transported to the hospital by ambulance because septic shock may occur after administration of the first dose of antibiotics.

On arrival at the emergency department, venous access should be ensured, and vital signs with oxygen saturation, a CBC with differential count and platelet count, and a metabolic profile should be obtained. No rectal temperatures should be taken, rectal examinations performed, or rectal medications administered because of the risk of generating a perianal or perirectal infection. However, careful examination of the mouth, oral mucosa, lungs, abdomen, and perineal/perianal area is important. A chest radiograph may be warranted if there are respiratory signs or symptoms, but its usefulness may be limited because the lack of neutrophils may not produce a visible infiltrate in patients who have severe neutropenia.

Anticipatory Guidance for the Patient Who Has Neutropenia

Parents of patients who have neutropenia need to contact a health-care practitioner at the onset of any febrile illness to assure prompt, appropriate care. The parents must know what is required for the evaluation (including the history and physical examination, blood counts and ANC, blood and other cultures) and the initial treatment (usual antibiotic recommendation and route of administration for their child) because they may not be near a major medical center, particularly when traveling. A per-

mission form may be necessary to allow carrying of injectable medications, such as G-CSF, syringes, and hypodermic needles on airplanes. Parents should carry a current written summary of the child's condition and laboratory values and the contact numbers of their primary institution and physicians.

It is important to maintain good oral hygiene and appropriate preventive dental visits, particularly for patients who have chronic neutropenia, to avoid chronic gingival or dental infection. Good skin care and prompt cleansing of superficial cuts, abrasions, and bruises where the skin is broken help to prevent local infection. All immunizations can and should be given according to the routine vaccination schedule, as long as the patient's neutropenia is not associated with an immunodeficiency syndrome. Children who have impaired T- or B-lymphocyte function should not receive live or attenuated-live vaccines. Recommendations for the administration of specific vaccines can be found in the American Academy of Pediatrics *Red Book*® and in the "Pink Book" produced by the Centers for Disease Control and Prevention, "Epidemiology and Prevention of Vaccine-preventable Diseases."

Child care and school attendance are reasonable for most children who have mild-to-moderate neutropenia, although contact with obviously ill children should be avoided. Children who have severe neutropenia or a history of serious infections with neutropenia require greater isolation to avoid exposure to infectious agents. Genetic counseling for the family of patients who have inherited neutropenias is indicated, and siblings should be tested for the disorder. Families of patients who have neutropenia may experience significant stress due to feeling responsible for the disease if it is an inherited condition or for exposing the child to infectious complications, caring for a child who has a chronic illness, and managing multiple physician and hospital visits. Most pediatric hematology/oncology units have social workers, parent advocates, and advanced-practice nurses who can provide the types of support services required by patients and their parents.

Summary

Neutropenia unrelated to chemotherapy toxicity occurs in a number of clinical settings. The most common conditions associated with neutropenia are those that are acquired, including viral infection, neutropenia associated with various medications, and immune neutropenia. Inherited neutropenias are rarer and often more profound. These disorders include the dominant or sporadic types of severe congenital neutropenia (often with mutations in the *ELA2* gene), the recessive type or Kostmann syndrome, and the marrow failure syndromes such as Fanconi anemia. Cyclic neutropenia may be severe at the nadir of the cycle. Of particular concern is the occurrence of fever in conjunction with neutropenia. This combination creates a medical emergency that must be addressed with appropriate evaluation and prompt administration of antibiotics. The actual risk of severe infection and the likelihood of recovery depend not only on the level of the ANC, but on the duration of the neutropenia. If recovery from the neutropenia is not expected, as in severe congenital types, G-CSF administration may be indicated.

To view an additional Suggested Reading list and figures related to this article, visit www.pedsinreview.org and click on Neutropenia in Pediatric Practice.

Suggested Reading

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

6. A 6-year-old boy presents with a history of a temperature to 103°F (39.4°C) and ulcerations on his lips and buccal mucosa 2 days ago. The child has some small, slightly ulcerated areas on his lips and is afebrile. His mother reports two similar episodes in the past 2 months. He has a white blood cell count of 2.9×10^3/mcL (2.9×10^9/L), hemoglobin of 11.4 g/dL (114 g/L), and platelet count of 349×10^3/mcL (349×10^9/L). His differential count is 40% neutrophils, 49% lymphocytes, 9% monocytes, and 2% eosinophils. Of the following, the *best* laboratory test to evaluate this child is:

   A. Antineutrophil antibodies.
   B. Blood counts two to three times a week for 4 to 6 weeks.
   C. Bone marrow aspiration.
   D. Herpes cultures.
   E. Repeat of the count in 1 week to see if it normalizes.

7. A previously well 3-year-old boy presents with 4 days of temperature up to 104°F (40°C). He is in no acute distress and does not appear ill. The only abnormal physical finding is mild rhinitis. A complete blood count reveals a white blood cell count of 1.5×10^3/mcL (1.5×10^9/L), hemoglobin of 12.8 g/dL (128 g/L), and platelet count of 349×10^3/mcL (349×10^9/L). His differential count is 2% neutrophils, 80% lymphocytes, 10% monocytes, and 6% eosinophils. A blood culture is obtained. After a single dose of acetaminophen, the child becomes afebrile. Of the following, the *most* appropriate next step is to:

   A. Give a dose of broad-spectrum antibiotics and admit the child for continuing intravenous antibiotics.
   B. Give a dose of ceftriaxone and see the child the following morning.
   C. Observe the child in the emergency department overnight.
   D. See the child the following morning but tell the parents to call sooner if he becomes more ill.
   E. Start amoxicillin and clavulanic acid orally and see the child the following morning.

8. The mother of a well 4-month-old child would like you to obtain a complete blood count to make sure her baby is "OK." You determine that she has no specific anxieties or reasons for suspecting a problem. Of the following, the *most* appropriate response is to:

   A. Explain that a routine complete blood count is obtained at 9 months of age.
   B. Explain that only a hemoglobin or hematocrit is measured routinely in well children at 9 to 12 months of age.
   C. Explain that there is no reason to obtain any blood counts for well children at any time.
   D. Order a complete blood count.
   E. Order a complete blood count with a differential white blood cell count.

9. What is the *most* common underlying cause for mild-to-moderate neutropenia?

   A. Exposure to medications such as antibiotics.
   B. Immune neutropenia.
   C. Shwachman-Diamond syndrome.
   D. Sequestration.
   E. Transient marrow suppression due to a viral infection.

10. At what age does alloimmune neutropenia usually resolve?

   A. 2 to 3 days.
   B. 2 to 3 weeks.
   C. 5 to 6 weeks.
   D. 2 to 3 months.
   E. 6 to 7 months.

Neutropenia in Pediatric Practice

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