How to Approach Neutropenia in Childhood

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Practice Gaps

1. Patients presenting with recurrent fevers, mouth ulcers and gingivitis should be evaluated for neutropenia.
2. The use of recombinant human granulocyte colony-stimulating factor (rhG-CSF) in the management of cyclic neutropenia and severe congenital neutropenia has dramatically decreased clinical symptoms and has decreased mortality from infectious causes.

Objectives

After completing this article, readers should be able to:

1. Recognize patients who have concerning features of history, physical examination, or laboratory results that warrant further investigation for possible neutropenia or other immunodeficiency.
2. Define mild, moderate, and severe neutropenia.
3. Understand that neutropenia can arise from acquired or intrinsic conditions. Know which causes of neutropenia are most commonly encountered in childhood.
4. Recognize why disorders of neutrophil production and release from the bone marrow carry more risk for bacterial infection than peripheral neutropenia associated with normal bone marrow morphology.
5. Understand why neutropenic patients undergoing immunosuppressive therapy are more at risk for a serious bacterial infection than patients who have isolated neutropenia.
6. Understand the impact that treatment with recombinant human granulocyte colony-stimulating factor has had on the outcome of patients who have severe congenital and cyclic neutropenia.
7. Know when to refer to a pediatric hematologist/oncologist.

A case study is provided to illustrate key aspects of the care of patients who have neutropenia.

Abbreviations:

AIN:	autoimmune neutropenia
AML:	acute myelogenous leukemia
ANC:	absolute neutrophil count
CBC:	complete blood cell count
MDS:	myelodysplastic syndrome
rhG-CSF:	recombinant human granulocyte colony-stimulating factor
SCN:	severe congenital neutropenia
SDS:	Shwachman-Diamond syndrome
WBC:	white blood cell count

Case

A 13-month-old boy presents to his primary care physician for his standard 1-year well-child check. He has had four episodes of otitis media since starting child care, all of which resolved with standard antibiotics. His mother reports that he has been healthy recently, with the exception of a viral upper respiratory tract infection that he and his older siblings experienced a few weeks ago. His physical examination is unremarkable, with no oral lesions, gingivitis, lymphadenopathy, hepatosplenomegaly, or rashes. He has normal forearms and thumbs. A screening complete blood cell count (CBC) with differential is obtained, which shows the following: white blood cell (WBC) count, 5.6/mm^3; hemoglobin, 13.8 g/dL; platelets, 212,000/mm^3; and absolute neutrophil count (ANC),

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300/mm³. Repeat CBC with differential 1 week later continues to show a normal total WBC count with persistent severe neutropenia. He is referred to a pediatric hematologist/oncologist for further evaluation and management. Antineutrophil antibody testing result is positive, and he is diagnosed as having autoimmune neutropenia of infancy.

This case represents a classic presentation of autoimmune neutropenia of infancy. The management usually is supportive because the risk for infection in 80% of the patients is no greater than that for normal children. More importantly, lymphocyte and monocyte function are normal; thus, affected children can receive live vaccines.

Introduction

The differential diagnosis for a patient presenting with recurrent infections and the question of an immunodeficiency is challenging. Similarities in the clinical presentation of neutrophil, antibody, and cellular immune defects, as well as complement disorders, can prove difficult for the physician attempting to establish a diagnosis. Infants and children who are brought to the pediatrician for "repeated infections" must be evaluated carefully. Most patients who have recurrent infections do not have an identifiable phagocyte defect or broader immunodeficiency. Instead, the patients often have anatomic variations, allergy-related illness, social exposures (such as child care), or other risk factors for recurrent infections. Given the low probability of identifying a discrete immune defect, the pediatrician faces the difficult decision of which patients merit a complete evaluation and referral to a pediatric immunologist or pediatric hematologist/oncologist.

In general, evaluations and referrals, particularly for neutrophil disorders, should be initiated for those who have had at least one of the listed clinical features in Table 1 within a 1-year period.

Once the decision is reached that an evaluation is warranted, a thorough clinical history, physical examination (including plotting a growth curve), and laboratory screening for immunodeficiency disorders should aid in determining the diagnosis. If the CBC reveals absolute neutropenia, further studies are required to establish the basis for the low ANC. Patients who experience recurrent bacterial infections but have a normal neutrophil count warrant evaluation for qualitative neutrophil disorders or other immunodeficiencies (Table 2). The remainder of this article will focus on neutropenia in childhood.

Table 1. Clinical Features Meriting Further Immunologic Evaluation

- More than two systemic bacterial infections (sepsis, meningitis, osteomyelitis)
- More than two serious respiratory infections (pneumonia)
- Multiple bacterial infections (cellulitis, draining otitis media, lymphadenitis)
- Unusual infections involving the liver or a brain abscess
- Infections caused by unusual pathogens (eg, *Aspergillus* pneumonia, disseminated candidiasis, infection with *Serratia marcescens*, *Nocardia* species, *Burkholderia cepacia*)
- Infections of unusual severity
- Chronic gingivitis or recurring aphthous ulcers

Neutropenia

Neutropenia is defined as a decrease in the absolute numbers of circulating segmented neutrophils and band forms in the blood. Obtaining a CBC with a differential count identifies this condition. The ANC is determined by multiplying the total WBC count by the percentage of segmented and band forms. The ANC for the general population normally ranges between 1.5 and 8.0 $\times$ 10^9/L. It is important to note that this normal range was generated primarily by using data from white children and may not be as applicable to other ethnic groups. For example, as many as 30% of the African-American population may have ANC levels as low as 0.8 $\times$ 10^9/L (0.8.0 $\times$ 10^9/L) and still be considered healthy.

Regardless of ethnicity, ANCs vary widely in healthy individuals. The relative proportion of neutrophils and lymphocytes in the blood changes with age. Neutrophils predominate at birth but decrease rapidly in the first few days after birth. During infancy, neutrophils constitute 20% to 30% of the circulating leukocyte populations. Approximately equal numbers of neutrophils and lymphocytes are found in the peripheral circulation by the time a child reaches ~5 years of age, and the characteristic 70% predominance of neutrophils that occurs in adulthood usually is attained at puberty. In healthy children, therefore, 20% to 70% of the total circulating WBCs may be neutrophils.

Individual patients who have neutropenia may be characterized as having acute or chronic neutropenia. Acute neutropenia is neutropenia of less than 3 months' duration, whereas chronic neutropenia is neutropenia of 4 or more months' duration. Severe acute neutropenia

Table 2. Causes and Mechanisms of Recurrent Infection in Primary Immunodeficiency States

Disorders	Deficiency
Humoral immunodeficiency (predominantly B-cell defects)	Impaired opsonization; failure of lysis and agglutination of bacteria; failure to neutralize bacterial toxins
Cellular immunodeficiency states (predominantly T-cell defects)	Absent T-cell cooperation for B-cell synthesis of antibodies to T cell–specific antigens
Severe combined immunodeficiency	Absent T-cell and B-cell response
Wiskott-Aldrich syndrome	Decreased antibody response to carbohydrate antigens
Ataxia-telangiectasia	T helper cell deficiency; immunoglobulin deficiency
Splenic insufficiency or absence	Defective opsonization; defective clearing of encapsulated organisms
Complement deficiencies	Defective opsonization
Neutrophil dysfunction syndromes, including chronic granulomatous disease and leukocyte adhesion deficiency	Impaired neutrophil bactericidal activity arising from failure to generate hydrogen peroxide by phagocytes; gingivitis, perirectal ulcers, delayed umbilical cord separation
Neutropenia ($<0.5 \times 10^9$/L)	Inadequate numbers of phagocytes

developing over hours or days and arising from chemotherapy, marrow failure, or marrow exhaustion often is associated with a greater risk of bacterial infection than severe chronic neutropenia. Chronic neutropenia arises from reduced production, increased destruction, or an excessive splenic sequestration of neutrophils.

Patients also can be defined as having mild neutropenia when the ANC is 1.0 to 1.5×10^9/L, moderate neutropenia when the ANC is 0.5 to 1.0×10^9/L, and severe neutropenia when the ANC is less than 0.5×10^9/L. (1) The classification of neutropenia as mild, moderate, or severe predicts the risk for pyogenic infections in patients who have neutropenia resulting from disorders of bone marrow production. Neutropenia associated with monocytopenia, lymphocytopenia, or hypogammaglobulinemia increases the risk for infection compared with isolated neutropenia. Neutropenia may be characterized further by whether it is acquired (Table 3) or arising from an intrinsic defect affecting production of myeloid progenitor cells (Table 4).

Susceptibility to bacterial infections, even in the presence of severe neutropenia, varies. In general, disorders of neutrophil production and release from the bone marrow carry more risk for bacterial infections than peripheral neutropenia associated with normal marrow morphology. Some patients who have chronic neutropenia and an ANC of less than 0.5×10^9/L do not experience serious infection, probably because other parts of their immune system remain intact, including T- and B-cell function, although they will often suffer from gingivitis.

In contrast, neutropenic patients receiving cytotoxic or immunosuppressive drugs, particularly in conjunction with malignancies, are more likely to develop serious bacterial infections than those whose neutropenia is isolated because the cytotoxic agents and immune suppression compromise both the function and numbers of lymphocyte and monocytes. Cancer chemotherapy also can compromise the integrity of the skin and mucous membranes as well as the nutritional status of the patient, which further predisposes the patient to infection.

Patients who have neutropenia are infected most frequently by endogenous flora. Colonization by various nosocomial organisms is also often observed. The types of pyogenic infections occurring most frequently among patients who have profound neutropenia are cellulitis and abscesses or furunculosis, pneumonia, and septicemia. In addition, stomatitis, gingivitis, perirectal inflammation, and otitis media are common. Occasionally, diffuse intestinal lesions develop, which can cause abdominal pain and diarrhea. These lesions may be related to bacterial overgrowth in the intestines. The most common pathogens isolated from patients who have neutropenia are *Staphylococcus aureus*, Gram-negative organisms, *Staphylococcus epidermidis*, streptococci, and enterococci.

Often, the signs and symptoms of local infections and inflammation, such as exudate, abscess formation, and regional lymphopathy, are diminished in neutropenic patients because of a paucity of neutrophils to mediate the inflammatory response. Other signs and symptoms, such as redness, pain, tenderness, and warmth,

Table 3. **Acquired Causes of Neutropenia**

Cause	Etiologic Factors/Agents	Associated Findings
Infection	Viruses, bacteria, protozoa, rickettsia, fungi	Redistribution from circulating to marginating pools, impaired production, accelerated destruction
Drug-induced	Phenothiazines, sulfonamides, anticonvulsants, penicillins, aminopyrine	Hypersensitivity reaction (fever, lymphadenopathy, rash, hepatitis, nephritis, pneumonitis, aplastic anemia), antineutrophil antibodies
Immune neutropenia	Alloimmune, autoimmune	Variable arrest from metamyelocyte to segmented neutrophils in bone marrow
Reticuloendothelial sequestration	Hypersplenism	Anemia, thrombocytopenia, neutropenia
Bone marrow replacement	Malignancy (eg, lymphoma, metastatic solid tumor)	Presence of immature myeloid and erythroid precursors in peripheral blood
Cancer chemotherapy or radiation therapy to bone marrow	Suppression of myeloid cell production	Bone marrow hypoplasia, anemia, thrombocytosis
Aplastic anemia	Stem cell destruction and depletion	Pancytopenia
Vitamin B_{12} or folate deficiency	Malnutrition; congenital deficiency of vitamin B_{12} absorption, transport, and storage; vitamin avoidance	Megaloblastic anemia, hypersegmented neutrophils
Acute leukemia, chronic myelogenous leukemia	Bone marrow replacement with malignant cells	Pancytopenia, leukocytosis
Myelodysplasia	Dysplastic maturation of stem cells	Bone marrow hypoplasia with megaloblastoid red cell precursors, thrombocytopenia
Prematurity with birthweight <2 kg	Impaired regulation of myeloid proliferation and reduced size of postmitotic pool	Maternal preeclampsia
Chronic idiopathic neutropenia	Impaired myeloid proliferation and/or maturation	None
Paroxysmal nocturnal hemoglobinuria	Acquired stem cell defect to secondary to mutation of *PIG-A* gene	Pancytopenia, thrombosis

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accompanied by fever, are mediated by inflammatory cytokines and generally are present.

Evaluation of Children Who Have Neutropenia

Evaluation begins with confirmation of neutropenia according to age-appropriate standards of neutrophil counts. When patients have ANCs less than 1.0×10^9/L, a manual differential count should be requested to determine whether blasts or immature neutrophils are present in the peripheral smear, which might indicate acute leukemia. The general pediatrician should obtain a thorough history to establish the onset of neutropenia; the type, frequency, and severity of infections; drug history for toxic exposures; and family history of recurrent infection or unexplained infant deaths.

The physical examination should note growth and development; phenotypic abnormalities; and the presence of bacterial infections at various sites in the body, including mucous membranes, gingiva, skin, tympanic membranes, and rectum. Lymphadenopathy, hepatosplenomegaly, and signs of possible underlying disease also should be noted. The presence of petechiae and purpura suggesting thrombocytopenia might indicate a more generalized disease process. The patient's temperature should be recorded, but rectal temperatures should be avoided in the neutropenic patient to prevent possible injury to the mucous membranes and subsequent spread of bacteria into the circulation.

The severity and duration of the neutropenia determine the extent of laboratory evaluation. If the child

Table 4. Intrinsic Disorders of Myeloid Precursor Cells

Syndrome	Inheritance (Gene)	Clinical Features (Including Static Neutropenia Unless Otherwise Noted)
Primary disorder of myelopoiesis		
Cyclic neutropenia	AD *(ELA2)*	Periodic oscillation (21-day cycles) in ANC
Severe congenital neutropenia	AD *(ELA2, GFL1, others)* X-linked *(WAS)*	Risk of MDS and AML neutropenic variant of WAS
Kostmann syndrome	AR *(HAX1)*	Neurologic abnormalities, risk of MDS and AML
Disorders of ribosomal function		
Shwachman-Diamond syndrome	AR *(SBDS)*	Pancreatic insufficiency, variable neutropenia, other cytopenias, metaphysical dysostosis
Dyskeratosis congenita	Telomerase defects: XL *(DKC1)*, AD *(TER)*, AR *(TERT)*	Nail dystrophy, leukoplakia, reticulated hyperpigmentation of the skin; 30%–60% develop bone marrow failure
Disorders of granule sorting		
Chédiak-Higashi syndrome	AR *(LYST)*	Partial albinism, giant granules in myeloid cells, platelet storage pool defect, impaired natural killer cell function, hemophagocytic lymphohistiocytosis
Griscelli syndrome, type II	AR *(RAB27a)*	Partial albinism, impaired natural killer cell function, hemophagocytic lymphohistiocytosis
Cohen syndrome	AR *(COH1)*	Developmental delay, facial dysmorphism, retinopathy
Hermansky-Pudlak syndrome, type II	AR *(AP3P1)*	Cyclic neutropenia, partial albinism
p14 deficiency	Probable AR *(MAPBPIP)*	Partial albinism, decreased B and T cells
Disorders of metabolism		
Glycogen storage disease type 1b	AR *(G6PT1)*	Hepatic enlargement, growth retardation, impaired neutrophil motility
Glucose-6-phosphate catalytic subunit 3 deficiency	AR *(G6PC3)*	Structural heart defects, urogenital abnormalities, venous angiectasia
Barth syndrome	XL *(TAZ1)*	Episodic neutropenia, dilated cardiomyopathy, methylglutaconic aciduria, pancytopenia
Pearson syndrome	Mitochondrial (DNA deletions)	Vacuolization of erythroid and myeloid precursors, ringed sideroblasts, pancytopenia
Neutropenia in disorders of immune function		
Common variable immunodeficiency	Familial sporadic (TNFRSF13B)	Hypogammaglobulinemia, other immune system defects
IgA deficiency	Unknown (Unknown or TNFRSF13B)	Decreased IgA
Severe combined immunodeficiency	AR, XL (multiple loci)	Absent humoral and cellular immune function
Hyper-IgM syndrome	XL (HIGM1)	Absent IgG, elevated IgM, autoimmune cytopenia
WHIM syndrome	AD (CXCR4)	Warts, hypogammaglobulinemia, infections, myelokathexis (WHIM)
Cartilage-hair hyperplasia	AR (RMKP)	Lymphopenia, short-limbed dwarfism, metaphysical chondrodysplasia, fine sparse hair
Schimke immune-osseous dysplasia	Probable AR (SMARCAL1)	Lymphopenia, pancytopenia, spondyloepiphyseal dysplasia, growth retardation, renal failure

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AD=autosomal dominant; AML=acute myelogenous leukemia; ANC=absolute neutrophil count; AR=autosomal recessive; Ig=immunoglobulin; MDS=myelodysplastic syndrome; WAD=Wiskott-Aldrich syndrome; XL=X linked.

is neutropenic at the time of examination shortly after a viral infection, a CBC should be performed 3 to 4 weeks later to evaluate recovery of the ANC. For the infant who remains asymptomatic despite the persistence of neutropenia, studies should be initiated to determine whether the patient's serum contains antineutrophil antibody. Bone marrow examination usually is not needed in the patient who has acute-onset neutropenia, is not experiencing more than the usual childhood bacterial infections, and who has no history of chronic gingivitis or recurrent mouth ulcers.

In contrast, children who have a clinical history consistent with infections due to chronic neutropenia, such as gingivitis in infancy, require more extensive evaluation by a pediatric hematologist/oncologist (Table 5). The specialist will obtain weekly CBCs for 6 weeks to establish whether there is a cycle of 21 days (±4 days) of neutropenia, which differentiates cyclic neutropenia from severe congenital neutropenia. Bone marrow aspirate and bone marrow cytogenetics are required to evaluate the risk for leukemia as well as to assess cellular morphology and the extent of myeloid cell maturation.

Children presenting with pancytopenia require a bone marrow aspiration and biopsy to aid in the diagnosis and to assess bone marrow cellularity. Additional marrow studies, including cytogenetic analysis, flow analysis, and special stains for detecting leukemia and other malignant disorders, are required in certain cases. Selection of other laboratory tests is determined by the duration and severity of the neutropenia and by the findings obtained on the physical examination.

Children who present with a history consistent with malabsorption and neutropenia should be evaluated for Shwachman-Diamond syndrome (SDS). These patients also require studies to evaluate the status of their pancreatic enzymes, as well as skeletal evaluation to assess the possibility of metaphyseal chondrodysplasia. All children who have chronic neutropenia associated with recurrent infections should have growth curves plotted to evaluate the effect of the infections on their growth. Antinuclear antibody determination, red blood cell folate concentration, and serum vitamin B_{12} level assessments are indicated for patients in whom collagen vascular disease (antinuclear antibody) and nutritional deficiencies (folate, vitamin B_{12}) are suspected. More extensive immunologic evaluation by a pediatric immunologist is indicated for selected patients suspected of having a concurrent immunodeficiency.

Acquired Neutropenias

Infection

A large number of acquired conditions may be associated with neutropenia (Table 3). Acute neutropenia evolves over a few days and occurs when neutrophil use is rapid and production is compromised. Infectious diseases are among the most common causes of acute neutropenia in children, with viral infection being the major cause of acute neutropenia in childhood. Viruses commonly causing neutropenia include respiratory syncytial virus, varicella, influenza A and B, measles, rubella, and Epstein-Barr virus. Neutropenia occurs often during the first 24 to 48 hours of illness and usually persists for 3 to 8 days, which corresponds to the period of acute viremia. Significant neutropenias may be associated also with bacterial, protozoal, rickettsia, and severe fungal infections.

The mechanisms responsible for neutropenia in acute bacterial infections include: 1) redistribution of neutrophils from the peripheral blood circulating pool to the marginating pool (neutrophils adherent to endothelium of low-flow exchange vessels) after release of cytokines that increase expression of the protein's intracellular adhesion molecule-1 and -2 on endothelium; 2) increased use of neutrophils at sites of infection; and 3) in some cases, decreased production of neutrophils. Sepsis is a particularly serious cause of neutropenia, especially among babies and children. Premature neonates are especially prone to exhausting their marrow reserve pool of segmented neutrophils and bands and rapidly succumbing to bacterial sepsis. In contrast, marrow reserves in older children and adults can increase during infection.

Drug-induced Neutropenia

Drugs can induce severe neutropenia by immunologic, toxic, and hypersensitivity-mediated mechanisms; often the mechanism is incompletely understood. This form of neutropenia must be distinguished from that seen with viral infections and from the severe neutropenia that accompanies administration of large doses of cytotoxic drugs or which follows radiation therapy. Only 10% of drug-induced neutropenia occurs in children. The higher frequency in adults aged older than 60 years likely reflects the use of multiple medications.

Once neutropenia occurs, the most effective therapeutic measure is withdrawal of nonessential drugs, particularly drugs suspected of being myeloid-toxic. Often, the neutropenia will respond to withdrawal of the offending drug. If the neutropenia fails to improve with drug withdrawal and the patient subsequently experiences signs and symptoms related to severe neutropenia, subcutaneous administration of 5 μg/kg of recombinant human granulocyte colony-stimulating factor (rhG-CSF) should be considered.

Immune Neutropenia

Immune neutropenias are associated with the presence of circulating antineutrophil antibodies. The antibodies are

Table 5. Diagnostic Approach for Patients Who Have Leukopenia

Evaluation	Associated Clinical Diagnosis
Initial evaluation by the generalist	
History of acute or chronic neutropenia	
General medical history	
Physical examination: stomatitis, gingivitis, dental defects, congenital anomalies	Congenital syndromes (Shwachman-Diamond, Wiskott-Aldrich, Fanconi anemia, dyskeratosis congenita, glycogen storage disease type Ib, disorders of vesicular transport, glucose-6-phosphate catalytic subunit 3 deficiency, immunodeficiencies
Spleen size	Hypersplenism
History of drug exposure	Drug-associated neutropenia
Complete blood count with differential and reticulocyte counts	Neutropenia, aplastic anemia, autoimmune cytopenias
If ANC <1,000/μL	
Evaluation of acute-onset neutropenia	
Repeat blood counts in 3–4 weeks	Transient myelosuppression (eg, viral)
Serology and cultures for infectious agents	Active chronic infection with viruses (eg, EBV, CMV), bacteria, mycobacteria, rickettsia
Discontinue drug(s) associated with neutropenia	Drug-associated neutropenia
Test for the presence of antineutrophil antibodies and occasionally test for antibodies to red cells and platelets	Autoimmune neutropenia, Evans syndrome
Measure quantitative Igs (G, A, and M), lymphocyte subsets	Neutropenia associated with disorders of immune function
If ANC <500 /μL on three separate tests	
Bone marrow aspiration and biopsy, with cytogenetics	Severe congenital neutropenia, cyclic neutropenia, Shwachman-Diamond syndrome, myelokathexis; chronic or benign or idiopathic neutropenia
Serial CBCs (3/week for 6 weeks)	Cyclic neutropenia
Exocrine pancreatic function	Shwachman-Diamond syndrome
Skeletal radiographs	Shwachman-Diamond syndrome, cartilage-hair hypoplasia, Fanconi anemia
If ALC <1,000/μL	
Repeat blood counts in 3-4 weeks	Transient leukopenia (eg, viral)
If ALC <1,000/μL on three separate tests	
HIV-1 antibody test	HIV-1 infection, AIDS
Quantitative Igs (G, A, and M), lymphocyte subsets	Congenital or acquired disorders of immune function
If there is pancytopenia	
Bone marrow aspiration and biopsy	Bone marrow replacement by malignancy, fibrosis, granulomata, storage cells
Bone marrow cytogenetics	Myelodysplasia, leukemia
Vitamin B_{12} and folate levels	Vitamin deficiencies

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ALC=absolute lymphocyte count; ANC=absolute neutrophil count; CBC=complete blood count; CMV=cytomegalovirus; EBV=Epstein-Barr virus; HIV=human immunodeficiency virus; Ig=immunoglobulin.

directed against specific neutrophil antigens genetically controlled independently of the human leukocyte antigen system. The antibodies mediate neutrophil destruction by complement-mediated lysis or splenic phagocytosis of antibody-coated neutrophils. The assays used most commonly to detect neutrophil antibodies are indirect immunofluorescence assays that identify surface antigens on the neutrophil and microcapillary agglutination assays that evaluate the ability of the antibody to clump neutrophils. Usually a combination of immunofluorescence and microcapillary agglutination assays, along with a panel of fresh neutrophils with known antigen specificity, are used to ensure identification of the antineutrophil antibodies. Often, neutrophil

antibodies are present at low titers or bind to neutrophil-specific antigens with low avidity. Thus, neutrophil antibody testing may require up to three attempts to achieve detection.

The presence of antibodies directed against red blood cell and platelet antigens and occasionally neutrophil antigens characterize Evans syndrome. These antibodies can lead to pancytopenia. The disorder is frequently seen in common variable immunodeficiency and other immunodeficiency states. Treatment relies on administration of prednisone to improve the blood counts. Management decisions are best made under the direction of a pediatric hematologist/oncologist.

Alloimmune Neonatal Neutropenia

This form of neonatal neutropenia occurs after transplacental transfer of maternal alloantibodies directed against an antigen of the infant's neutrophils. This disorder is present in 0.2% of pregnancies. (2) Prenatal sensitization induces maternal immunoglobulin G antibodies to neutrophil antigens of the fetal cells. Symptomatic infants may present with delayed separation of the umbilical cord, mild skin infections, fever, and pneumonia within the first 2 weeks after birth; these conditions resolve with antibiotic therapy. The neutropenia often is severe and associated with fever and infections due to the usual microbes that cause neonatal disease. By 7 weeks after birth, the infant's neutrophil count generally returns to normal, reflecting the duration of survival of the maternal antibody in the infant's circulation. Usually, treatment consists of supportive care and appropriate antibiotics for infections. If the infection is severe, rhG-CSF may be used.

Autoimmune Neutropenia of Infancy

Primary autoimmune neutropenia (AIN) is observed most commonly in infants and is caused by granulocyte-specific autoantibodies. In many patients, AIN is diagnosed only after an expensive and burdening investigation and unnecessary treatment with rhG-CSF, as AIN is not well known among physicians. Primary AIN is diagnosed typically in infants between the ages of 5 and 15 months. In 90% of infants, AIN is not associated with an increased risk of repeated pyogenic infections, even in the presence of severe neutropenia. Previously, many of these patients were categorized as having chronic benign neutropenia of childhood. Typically, 95% of infants undergo spontaneous remission within 7 to 30 months.

Often, screening must be repeated for antibodies several times until the antibodies are detected, because they are not always observed in the serum. The bone marrow typically is normocellular or hypercellular and usually contains a reduced number of segmented neutrophils. Symptomatic treatment with antibiotics is satisfactory in most infants. Among patients treated with rhG-CSF for severe infection or for surgical preparation, neutrophil counts may be increased.

When history is combined with the detection of neutrophil-specific antibodies, most patients can be diagnosed readily without stressful investigations, including the need for bone marrow aspiration. Most importantly, these infants can be immunized with live viral vaccines because the cellular immune system is intact, which includes normal T- and B-cell function.

Sequestration/Hypersplenism

Splenic enlargement resulting from intrinsic splenic disease, such as storage diseases or systemic disorders that cause splenic hyperplasia arising from inflammation, neoplasia, or hemolytic anemias, can lead to neutropenia. Most often, the neutropenia is mild to moderate and is accompanied by corresponding degrees of thrombocytopenia and anemia. Cytopenias often are improved by successfully treating the underlying disease. In selected cases, splenectomy may be a necessary option to restore the neutrophil count, but this procedure results in increased risk for infections by encapsulated bacterial infections. Splenectomy should be avoided in patients who have combined variable immunodeficiency because of the high risk for predisposing the patient to sepsis.

Marrow Replacement, Cancer Chemotherapy and Radiation Effects, and Aplastic Anemia

As seen in Table 3, various acquired bone marrow disorders lead to neutropenia and are accompanied by anemia and thrombocytopenia. Hematologic malignancies and metastatic solid tumors suppress myelopoiesis by infiltrating the bone marrow. Neutropenia often accompanies myelodysplastic disorders, which are characterized by peripheral cytopenias and macrocytic blood cells. Cancer chemotherapy and radiation to the bone marrow can damage bone marrow stem cells and prevent their development into mature neutrophils, red blood cells, and platelets. Aplastic anemia can arise from T cell–mediated damage to stem cells, leading to neutropenia and other cytopenias.

Management of acquired transient neutropenia associated with malignancies, chemotherapy, or immunosuppressive chemotherapy requires prompt attention to the treatment of infections with broad-spectrum antibiotics to cover *S aureus* and *Pseudomonas aeruginosa*. Frequently, the infections are heralded only by fever, and sepsis can cause early death. Empiric treatment of fever

with broad-spectrum antibiotics is imperative, even before the results of blood cultures are known.

Ineffective Myelopoiesis

Ineffective myelopoiesis may result from congenital or acquired vitamin B_{12} or folic acid deficiency. Although vitamin deficiencies are rare in pediatrics, neutropenia may appear in an infant who has starvation or marasmus and in adolescents who have anorexia nervosa or have experienced extended use of antibiotics, such as trimethoprim-sulfamethoxazole, which can lead to folate deficiency.

Intrinsic Disorders of Myeloid Cell Maturation and Proliferation

The intrinsic disorders of proliferation and maturation of myeloid stem cells are rare (Table 4). Affected patients frequently benefit from rhG-CSF therapy. Congenital disorders that have severe neutropenia as a clinical feature include severe combined immunodeficiency syndromes, hyper–immunoglobulin M syndrome, common variable immunodeficiencies, glycogen storage disease type 1b, SDS, cyclic neutropenia, and severe congenital neutropenia.

Cyclic Neutropenia

Cyclic neutropenia is a rare congenital granulopoietic disorder. The mode of inheritance is autosomal dominant, and the disorder is characterized by regular, periodic oscillations, with the number of peripheral neutrophils ranging from normal to neutropenic values. The nadir of the neutropenia count is accompanied by an elevated monocyte count. The reciprocity between the neutrophil and monocyte counts allows for differentiation from idiopathic neutropenia, in which such a relationship does not exist. The mean oscillatory period of the cycle is 21 days (±4 days) of profound neutropenia.

The estimated frequency of this condition is ~0.6 per 1 million. Cyclic neutropenia arises from a mutation in the neutrophil elastase gene. Patients may experience oral ulcers, stomatitis, or cutaneous infections associated with lymph node enlargement during the neutropenic phase. Occasionally, patients develop severe abdominal pain from different intestinal lesions. Serious infections occur occasionally and may lead to pneumonia or recurrent ulcerations in the oral, vaginal, and rectal mucosa.

Approximately 10% of patients who had cyclic neutropenia before the availability of rhG-CSF developed fatal *Clostridium perfringens* or Gram-negative infection, likely arising from dissemination of organisms from ulcers or translocation of bacteria from the gastrointestinal tract. Cyclic neutropenia frequently is called cyclic hematopoiesis because of the cycling of other blood cells, such as platelets, reticulocytes, and monocytes.

Cyclic neutropenia is diagnosed by obtaining blood counts two to three times a week for 2 months. The requirement for repeated blood counts is necessary because some of the elastase mutations overlap with those in patients who have severe congenital neutropenia. The diagnosis can be confirmed with molecular genetic studies demonstrating mutations in the elastase gene. Affected patients are treated with daily rhG-CSF, and their cycle of profound neutropenia changes from a 21-day interval to a 9- to 11-day interval with 1 day of profound neutropenia. Such patients no longer are at risk for fatal infections with *Clostridia* or Gram-negative organisms, and antibiotic use associated with inflammatory disease is diminished. (3)

Severe Congenital Neutropenia

Severe congenital neutropenia (SCN) is characterized by an arrest in myeloid maturation at the promyelocyte stage of the bone marrow, resulting in an ANC of less than 0.2×10^9/L on at least three separate occasions over a 1-month period. The disorder occurs with a frequency of 1 per 1 million. This condition is inherited both as an autosomal dominant disorder, which is associated with mutation in the elastase gene in 60% of patients, and as an autosomal recessive disorder in consanguineous populations. The autosomal recessive disorder is commonly called Kostmann disease. Many other genetic causes of congenital neutropenia disorders have been identified (Table 4).

Patients who have SCN experience a predictable pattern of infection and inflammation. Mouth ulcers, gingivitis, otitis media, respiratory infections, cellulitis, and skin abscesses are the most common conditions. Pneumonia and deep tissue abscesses occur frequently and are life-threatening.

The onset of mouth ulcers and gingivitis, the most common finding, occurs in early childhood. Mild hepatosplenomegaly is common. Peripheral blood eosinophilia and monocytosis and a bone marrow test result demonstrating arrest of myeloid cell maturation at the promyelocyte stage are associated with profound neutropenia. The observed "maturational arrest" in the bone marrow differentiates SCN from idiopathic and immune neutropenia. The platelet count often is mildly elevated, and patients have anemia associated with chronic inflammatory disease. In the past, two-thirds of patients died of fatal infections before reaching adolescence. rhG-CSF has had a major impact on the management and outcomes of SCN in that morbidity and mortality from infectious complications have been significantly diminished. (3)

Before the availability of rhG-CSF, leukemic transformation occurred in some surviving patients diagnosed as having SCN and SDS. After many years of clinical use of rhG-CSF, it has been documented that ~10% to 20% of patients who are diagnosed as having SCN develop myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML), which appears independently from rhG-CSF use.

The onset of MDS can be insidious, with patients developing thrombocytopenia, anemia, or a change in the dose of rhG-CSF required to maintain the target ANC. Cytogenetic analysis of unstimulated bone marrow cells frequently documents loss of the entire chromosome 7 homolog (monosomy 7) or a partial deletion involving the long arm. Some patients have trisomy 21. Activating *ras* oncogene mutations have been identified retrospectively in patients who developed MDS/AML. At the minimum, CBCs with differential counts every 3 months and annual bone marrow aspirations with cytogenetic evaluation should be performed to adequately manage patients who have severe congenital neutropenia. It is important to differentiate cyclic neutropenia from severe congenital neutropenia. Patients who have cyclic neutropenia are not at risk for leukemia and do not require annual bone marrow studies.

Currently, more than 95% of patients who have SCN respond to rhG-CSF. The 5% of patients who do not respond to rhG-CSF with a sufficient increase in ANC should be considered as candidates for stem cell transplantation from a human leukocyte antigen–identical sibling or a matched unrelated donor. Additional scenarios that prompt consideration for stem cell transplantation include the requirement for high (greater than 8 μg/kg) rhG-CSF doses to maintain an adequate neutrophil count; detection of a cytogenetic abnormality or MDS on bone marrow evaluation; and, in rare instances, select gene mutations known to be associated with a high rate of leukemic conversion. For patients who have SCN and MDS/AML, traditional chemotherapy is ineffective and associated with high mortality. Stem cell transplantation has proven to be the only successful treatment once patients who have SCN convert to MDS/AML.

Therapy for fever in severe chronic neutropenia is dictated by the clinical manifestations and the degree of neutropenia. Superficial infections in children who have mild to moderate neutropenia may be treated with appropriate oral antibiotics. Patients who have neutropenia with an ANC of less than 0.5×10^9/L and fevers higher than 38°C should be hospitalized and receive broad-spectrum intravenous antibiotics.

Management of acquired transient neutropenia associated with malignancies, chemotherapy, or immunosuppressive chemotherapy requires prompt attention to the treatment of infections with broad-spectrum antibiotics to cover *S aureus* and *P aeruginosa*. Frequently, the infections are heralded only by fever, and sepsis is a cause of early death. Empiric treatment of fever with broad-spectrum antibiotics is imperative even before the results of blood cultures are known.

Summary

- Patients presenting with recurrent fevers, mouth ulcers, and gingivitis should be evaluated for neutropenia.
- Neutropenia can be defined as mild when the absolute neutrophil count (ANC) is 1.0 to $1.5 \times 10^3/\mu$L ($1.0–1.5 \times 10^9$/L), moderate when the ANC is 0.5 to $1.0 \times 10^3/\mu$L ($0.5–1.0 \times 10^9$/L), and severe when the ANC is less than $0.5 \times 10^3/\mu$L (0.5×10^9/L).
- The most commonly encountered causes of neutropenia in childhood are viral-induced neutropenia and immune-mediated neutropenia.
- Patients who have disorders of neutrophil production and release from the bone marrow carry a greater risk of bacterial infection than patients who have peripheral neutropenia associated with a normal bone marrow because the bone marrow is not able to produce new neutrophils sufficiently in times of need (ie, infection).
- Patients receiving immunosuppressive therapy (eg, chemotherapy) are at significantly higher risk for serious bacterial infection compared with those who have isolated neutropenia due to the compounding T-cell and B-cell dysfunction.
- The use of recombinant human granulocyte colony-stimulating factor in the management of cyclic neutropenia and severe congenital neutropenia has dramatically decreased clinical symptoms and has decreased mortality from infectious causes.

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1. A previously well 2-year-old white boy has had a fever for 2 days. He has had no other symptoms. His examination is normal. An emergency department physician orders a complete blood count and differential with the following results: white blood cell count, 4,326/mm^3 (4.326 × 10^9/L); neutrophils, 10%; bands, 1%; lymphocytes, 78%; monocytes, 7%; eosinophils, 2%; and basophils, 2%. This patient has:
   A. A normal neutrophil count
   B. Lymphopenia
   C. Mild neutropenia
   D. Moderate neutropenia
   E. Severe neutropenia

2. Which finding usually associated with inflammation is most likely to be absent in a severely neutropenic 3-year-old girl with a community-acquired methicillin-resistant *Staphylococcus aureus* infection of her forearm?
   A. Abscess formation
   B. Erythema
   C. Fever
   D. Tenderness
   E. Warmth

3. Which of the following infants is most likely to have an underlying condition associated with clinically significant neutropenia? A 6-month-old boy with a history of:
   A. A single bout of enterococcal urinary tract infection
   B. A single bout of enteroviral meningitis
   C. A single bout of *S aureus* septic arthritis
   D. Recurrent aphthous ulcers
   E. Recurrent wheezing

4. Which of the following patients who has severe neutropenia will have the best outcome without treatment? A 12-month-old girl:
   A. Receiving chemotherapy for acute lymphoblastic leukemia
   B. Who has autoimmune neutropenia of infancy
   C. With cyclic neutropenia
   D. With Kostmann disease
   E. With Shwachman-Diamond syndrome

5. Recombinant human granulocyte colony-stimulating factor is most effective in correcting the neutropenia of patients who have:
   A. Autoimmune neutropenia of infancy
   B. Myelodysplastic syndrome/acute myelogenous leukemia
   C. Sequestration/hypersplenism
   D. Severe congenital neutropenia
   E. Severe influenza infections

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