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Evaluation and Management of Patients with Isolated Neutropenia

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Abstract

Neutropenia, defined as an absolute neutrophil count below 1.5×10^9/L, encompasses a wide range of diagnoses, from normal variants to life-threatening acquired and congenital disorders. This review addresses the diagnosis and management of isolated neutropenia, not multiple cytopenias due to splenomegaly, bone marrow replacement, or myelosuppression by chemotherapy or radiation. Laboratory evaluation generally includes repeat complete blood counts with differentials and bone marrow examination with cytogenetics. Neutrophil antibody testing may be useful, but only in the context of clinical and bone marrow findings. The discovery of genes responsible for congenital neutropenias now permits genetic diagnosis in many cases. Management of severe chronic neutropenia includes common-sense precautions to avoid infection; aggressive treatment of bacterial or fungal infections; and administration of granulocyte colony-stimulating factor (G-CSF). Patients with severe congenital neutropenia, particularly those who respond poorly to G-CSF, have a risk of eventually developing myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) and require monitoring for this complication, which can also occur without G-CSF therapy. Patients with cyclic, idiopathic and autoimmune neutropenia have virtually no risk of evolving to MDS or AML. Hematopoietic stem cell transplantation is a curative therapy for congenital neutropenia with MDS/AML or with cytogenetic abnormalities indicating impending conversion.

Introduction

Neutropenia, usually defined as an absolute neutrophil count (ANC) below 1.5×10^9/L ($1500/mm^3$), encompasses a wide range of diagnoses, from normal variants to life-threatening acquired and congenital disorders. The functional consequences depend largely, but not exclusively, on the severity of neutropenia: ANC of $1.0–1.5 \times 10^9$/L does not impair host defense, but may warrant investigation of the underlying cause; ANC of $0.5–1.0 \times 10^9$/L may slightly increase the risk of infections, but only if other arms of the immune system are impaired; ANC of $0.2–0.5 \times 10^9$/L is associated with an increased risk of infections in most patients. ANC of 0.2×10^9/L or less (often referred to as “agranulocytosis”) carries a risk of severe, life-threatening infections with susceptibility to opportunistic organisms.

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These oft-quoted criteria were derived from clinical experience with neutropenia secondary to cancer chemotherapy, so patients with isolated neutropenia and otherwise normal immune systems would be expected to have lower risks of infection at any ANC.

Healthy Caucasian and Asian populations generally have ANCs of 1.5 to 7.0 × 10^9/L. Persons of African descent, however, often have lower normal neutrophil counts, with ANC <1.5 × 10^9/L occurring in about 4.5% of black participants in one U.S. survey,[1] and associated with the Duffy negative blood group.[2] It was once thought that neutrophil levels fluctuate cyclically in the normal person, but best evidence now indicates that levels fluctuate considerably but do not normally cycle in a mathematically regular fashion.[3]

This review will address the diagnosis and management of isolated neutropenia, not multiple cytopenias due to splenomegaly, bone marrow replacement, or myelosuppression by chemotherapy or radiation. Other reviews summarize these disorders and their management.[4;5]

Classification of Neutropenia

Neutropenia can be described as transient (or “acute”) or chronic (or “persistent”); extrinsic or intrinsic; by descriptive names (e.g., neonatal isoimmune neutropenia of infancy, cyclic neutropenia, severe congenital neutropenia) and as syndromes (e.g., Kostmann, Shwachman-Diamond, and Barth syndromes). The discovery of the diverse causes for the congenital neutropenias now permits genetic diagnosis in many cases.

Transient and Chronic Neutropenia

Transient neutropenia is most commonly associated with viral infections.[6–8] Table 1 identifies some of the most important viral agents, but almost any viral infection can be associated with transient neutropenia. Infectious mononucleosis due to Epstein-Barr virus infection is a relatively common viral infection causing neutropenia.[4] Overwhelming bacterial infections, particularly in patients with alcoholism or underlying hematological diseases, may deplete bone marrow reserves and cause neutropenia, a dire sign in this setting. In acute malaria, neutropenia occurs due to a rapidly enlarging spleen.[9;10] Chronic bacterial infections and some inflammatory and autoimmune diseases (e.g., rheumatoid arthritis and sarcoidosis) are also associated with splenomegaly and neutropenia. (Table 1)

Chemotherapy agents and a wide variety of other medications cause transient isolated neutropenia; the drugs listed in Table 1 are the most common agents associated with isolated, idiosyncratic, drug-induced neutropenia.

Chronic neutropenia is usually defined as an ANC less than 1.5 × 10^9/L lasting for more than 3 months.[11] It is quite common for healthy individuals to have an occasional ANC value in the range of 1.5–2.0 × 10^9/L, especially with the counts performed early in the day. Some individuals in good health can have isolated counts even lower, i.e., 1.0–1.5 ×10^9/L. In these individuals, periodic complete blood cell counts are usually all that is needed for their initial evaluation. The primary purpose of serial counts and follow-up is to see if the ANC is chronically reduced and if, over time, other hematological abnormalities or evidence of an underlying infectious, inflammatory or malignant disease will appear. Discovery of lower neutrophils for any reason, i.e. ANC 0.5–1.0 × 10^9/L, is cause for an in-depth evaluation. In both children and adults, the most common diagnosis for counts in this range is autoimmune or idiopathic neutropenia. However, there are a number of other acquired and inherited causes (Table 2). Severe chronic neutropenia is a term for a category of diseases in which the ANC is consistently or regularly reduced to less than 0.5 × 10 9/L. The major sub-types are congenital, cyclic, idiopathic and autoimmune.[11] Patients with severe chronic

neutropenia need careful diagnostic testing because of the severity of infectious complications associated with this hematological abnormality.

It is important to note that blood neutrophil counts are not as stable as other blood cell counts or many other physiological measurements. Counts may vary considerably over short periods of time, associated with activity, exercise, eating or just the time of day. Counts vary even more with serious infections, inflammatory disorders, corticosteroid therapy or extreme anxiety. It is always important in the evaluation of blood neutrophil counts to consider the conditions when the blood sample was obtained and to have several measurements when defining the severity of acute or chronic neutropenia.[11]

Extrinsic and Acquired Causes of Chronic Neutropenia

Nutritional Neutropenias

Nutritional deficiencies of vitamin B12, folic acid or copper, or severe protein-calorie malnutrition can cause neutropenia. These deficiencies almost always cause multiple cytopenias rather than isolated neutropenia and are usually diagnosed based on medical history, physical examination and laboratory measurements of specific vitamin levels.

Immune and autoimmune neutropenias

Neonatal isoimmune neutropenia occurs in newborns with fetal/maternal neutrophil antigen incompatibility, leading to transplacental transfer of antibodies to specific epitopes expressed on the newborn's neutrophils. These most commonly involve alleles of the HNA-1a, HNA-lb and HNA-1c antigens (formerly termed NA1, NA2, and SH) that represent polymorphisms of Fc gamma receptor IIIb (FcγRIIIb; CD16b);[12;13] the disorder can also occur with maternal FcγRIIIb deficiency.[13] Neutropenia can be profound and lead to omphalitis, cellulitis, or sepsis. As with other isoimmune cytopenias, the process resolves spontaneously in about six weeks, with decay of the maternal antibody, but neutropenia can last as long as 6 months[11] Parental neutrophil antigen typing and infant neutrophil antibody testing can be useful to establish the diagnosis and predict the risk in future pregnancies. Autoimmune neutropenia in mothers may also cause neonatal neutropenia due to trans-placental transfer of IgG antibodies that are reactive with both the mother's and the child's neutrophils. This is an unusual condition, but it may be devastating because of the risk of severe infections in the newborn.

Chronic autoimmune neutropenia of infancy and early childhood is a relatively common disorder and virtually always runs a benign course, despite very low ANCs. It usually resolves spontaneously by age 3–5 years, with a mean duration of 17 months.[14;15] In most cases, neutropenia is detected during the occurrence of an acute febrile illness. With follow-up, the neutropenia persists after resolution of the illness that led to testing. Systematic studies indicate that many, but not all, of these children have autoantibodies directed against surface antigens of neutrophils.[14] From a clinical perspective the value of testing for autoantibodies in patients with moderate to severe neutropenia without evidence of recurrent fevers or infections is debatable. Testing is not widely available and, if done, it is best performed by a reference laboratory performing these assays frequently. Serial testing may give inconsistent results and patients with genetic as well as acquired neutropenia may have false positive test results.

In older children, chronic autoimmune neutropenia or multiple immune cytopenias should raise suspicion of a congenital immunological disorder such as autoimmune lymphoproliferative syndrome or common variable immunodeficiency.[16;17] Screening for these disorders can be performed by measurement of circulating T cell receptor alpha/beta

positive, CD4/CD8 double negative T cells or of serum immunoglobulins, respectively. Definitive diagnosis of these conditions requires specialized immunological testing.

In adult women, autoimmune and idiopathic neutropenia are relatively common, overlapping diagnoses, with a female to male ratio of about 5:1. Because of the lack of any definitive tests, the diagnoses “autoimmune neutropenia” and “idiopathic neutropenia” are used nearly synonymously. Ordinarily the neutropenia is recognized on a routine complete blood cell count, often without any history of recurrent fevers or infections. Often there is a mild reduction in the blood lymphocyte count with symmetrical, not selective, reduction in blood lymphocyte subtypes. The neutropenia may be mild, moderate or severe. Patients with more severe neutropenia are prone to recurrent fevers, upper respiratory infections and skin infections, but the infections are readily treated with antibiotics in most cases. With infections, the ANC may rise to a normal level. In typical cases, the diagnosis can be made from the history, physical examination and a series of complete blood cell counts. If a bone marrow examination is performed it may show a mild reduction in mature neutrophils and clusters of polyclonal lymphocytes. It is uncommon for patients presenting with this type of isolated neutropenia to have arthralgias, stiffness, fatigue or weight loss or laboratory test results suggesting a systemic autoimmune disease. It is also uncommon for these patients to progress to develop systemic lupus erythematosus, rheumatoid arthritis, Sjögren or Felty syndrome, or other systemic autoimmune diseases.[11]

Neutropenia also occurs as an integral part of systemic autoimmune diseases such as lupus erythematosus and rheumatoid arthritis. These diseases are diagnosed based on systemic symptoms and a constellation of disease-associated physical findings and specific immunological tests, e.g., antinuclear antibodies, rheumatoid factor, other autoantibodies. Typically, with the exception of Felty syndrome, neutropenia associated with the systemic autoimmune diseases is mild and best managed as part of treatment of the underlying disease. Transient (<24 hr) neutropenia often accompanies transfusion-related acute lung injury (“TRALI”) due to pulmonary trapping of recipient neutrophils opsonized by transfused alloantibodies or activated by soluble mediators.[18]

Neutropenia commonly accompanies, or can be a presenting feature of, large granular lymphocytic (LGL) leukemia,[19] in which cytokine-mediated inhibition of granulopoiesis combines with neutrophil destruction by both cell-mediated and humoral immune mechanisms. Other typical characteristics of the disease include lymphocytosis and splenomegaly. LGL leukemia diagnosis is based on the finding of clonal expansion (>0.5 × 10^9/L) of peripheral blood LGL with markers of activated T cells (e.g. $CD3^+/CD8^+/CD57^+$ and/or $CD16^+$ with clonal T cell receptor gene rearrangement) or NK cells (e.g. $CD3^-/CD8^+/CD16^+$ and/or $CD16^+/CD56^+$).[20]

Intrinsic neutropenias

The intrinsic neutropenias are due to genetic or acquired abnormalities in hematopoietic progenitor cells resulting in the failure of the bone marrow to produce mature neutrophils. They are either acquired or congenital (Table 2). Myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) are acquired disorders and rarely present as isolated neutropenia. However, patients with severe congenital neutropenia, as well as patients with other inherited marrow failure disorders, may develop MDS and AML; these cases are classified as secondary MDS/AML.

Congenital neutropenia has many causes and may occur either as an isolated manifestation of a single lineage disorder or in the setting of a multi-system syndrome. The congenital neutropenias are categorized by clinical/classical names or based on the name of the mutated gene known to cause the disease (Table 2).[5;21;22]

Severe congenital neutropenia (SCN) and cyclic neutropenia (CyN) are examples of well understood causes of severe chronic neutropenia that are usually still called by their original/classic names. Both diseases derive from excessive apoptosis of myeloid precursors early in development. In SCN, apoptosis at the promyelocyte stage of development leads to apparent "maturation arrest" in the bone marrow. The loss of cells early in their development results in "ineffective production" and severe neutropenia with ANCs usually below 0.5×10^9/L, and often lower. In CyN, bone marrow maturation, and hence peripheral blood neutrophil counts, follow a regular oscillating pattern with consistent, usually 21-day, periodicity. Most commonly, SCN is inherited as an autosomal dominant disorder and attributed to mutations in *ELANE* (formerly *ELA2*). This gene encodes neutrophil elastase, an abundant protein first expressed at high levels in promyelocytes.[23;24] Most mutations are missense or splicing defects that produce an abnormal protein product, resulting in apoptosis through the unfolded protein response.[25;26] Most cases of CyN are also attributable to *ELANE* mutations. Because the same gene is responsible for both diseases – with some mutations associated with both phenotypes,[24] even in the same kindred[27] – the combined entity has also recently been called "*ELANE* associated neutropenia."

Autosomal recessive SCN can be caused by defects in several genes, including *HAX1*, an anti-apoptotic gene that is responsible for the classic "Kostmann syndrome," and *G6PC3*, which encodes a neutrophil-specific catalytic subunit of glucose-6-phosphatase.[28;29] By contrast with *ELANE*, which is expressed selectively in myeloid cells, these genes are broadly expressed in many tissues and organs. As a result, some patients with HAX1 protein defects have associated neurological deficits, and *G6PC3* defects were originally described in a cohort of patients with cardiac anomalies, urogenital abnormalities, and venous angiectasias. Both *HAX1* and *G6PC3* mutations can also be responsible for isolated neutropenia without an extended phenotype.[30;31] Very rare forms of SCN result from mutations in *GFI1* (autosomal dominant) and *WAS* (X-linked, gain of function mutations).[21;32;33] Approximately 60% of patients with a diagnosis of severe congenital neutropenia can now be given a precise genetic diagnosis.

Clinical Evaluation

Careful medical history and family history are the initial steps in evaluating patients with neutropenia or recurrent infections suggesting isolated neutropenia. It is important to know the frequency of illness, the severity of fever and other constitutional symptoms, the presence or absence of oral inflammation (mouth ulcers, gingivitis, periodontitis, tooth loss and replacement), and the presence or absence of other common infectious problems of patients with neutropenia (cellulitis, sinusitis, otitis, pharyngitis, pneumonia, gastrointestinal symptoms, perirectal infections and sepsis or evidence of deep tissue infections). It is also important to know how these problems have been previously managed and the patient's antibiotic exposures. A history of viral infections, other symptoms suggesting immunodeficiency, and general health, growth and development are also very important.

Because many defects in host defenses including neutropenia are heritable, family history is also important beginning with an understanding of the medical history of the patient's immediate family, and extending as far as possible, especially if there are clues that other family members may have similar symptoms, laboratory findings or may have died from infections or hematological malignancies. It is important to note that the severity of illness may vary within families with the same genetic cause for neutropenia. Relatives of patients with very severe neutropenia may have ANC levels of 0.5–1.5 × 109/L and relative few symptoms and still have the same underlying genetic disease. Unexplained infant deaths may also indicate an inherited form of neutropenia.

The physical examination may reveal mouth ulcers, abnormal teeth and gums, and evidence of acute or chronic sinusitis, pharyngitis, or otitis. Careful examination of the chest and abdomen is very important. Acute abdominal pain and fever in neutropenic patients should raise concerns about neutropenic colitis and sepsis from an abdominal source. The perirectal and anal area should also be examined carefully because patients with severe neutropenia often develop cellulitis, including necrotizing cellulitis due to infection with *Clostridial species* and other anaerobic organisms, in this area. Because neutropenia is associated with a reduced inflammatory response with less than typical pain and redness, it is important to examine and reexamine the patient carefully.

Laboratory Evaluation

CBC—Neutropenia is usually discovered with a complete blood cell count (CBC) and leukocyte differential count (Diff), done either as a part of evaluation of a patient for acute or recurrent fever and infection, or as part of a general health examination. In a patient with mild neutropenia and no other health or hematological problems, a follow-up CBC and Diff may be all that is necessary. The medical history and the severity of neutropenia with the initial counts generally direct further evaluation. Every opportunity should be made to capture information from previous CBCs and Diffs, generally by asking the patient to request this information from all previous providers. It is particularly important to retrieve counts from very early in life, if possible.

To determine the severity and duration of neutropenia, at least three determinations over three months are a minimum. If CyN is part of the differential diagnosis – due to family history, highly variable past neutrophil counts, or regularly recurrent fever or mouth ulcers – then a CBC and differential count should be obtained at least three times per week for four to six weeks (i.e. more than one, preferably two, 21 day cycles). In CyN, reciprocal oscillations of monocytes often occur; reticulocyte, lymphocyte, eosinophil, and platelet numbers may also show cyclical variation.[34]

Bone marrow examination—A bone marrow examination is valuable to identify abnormalities in myelopoiesis in neutropenic patients. Initially it may be critical to look for excess myeloblasts and other markers of MDS and AML. If there is concern about MDS or AML, cytogenetic examination of the marrow specimen is also useful. A marrow smear is particularly useful to identify the stage of the defect in myelopoiesis causing neutropenia. For example, patients with severe congenital neutropenia due to *ELANE* or *HAX1* mutations usually have “maturation arrest” with a generous number of promyelocytes but only a few mature myeloid cells.[23;28] At the other extreme, patients with myelokathexis have abundant “hypermature” neutrophils in the bone marrow, because the cells had difficulty exiting the marrow and entering the blood. In patients with cyclic neutropenia, the cellularity of the marrow and the marrow differential count depend on the timing in the neutrophil cycle when the sample is obtained. In fact, serial sampling shows the proliferative response and the accumulation of mature neutrophils in the marrow that precedes the recovery phase for neutrophils in the blood.[34] Careful examination of both bone marrow and peripheral blood smears, plus bone marrow cytogenetics, are essential before a patient is treated with hematopoietic growth factors, in order to have a patient-specific reference for subsequent comparisons.

As a part of their long-term care, it is recommended that patients with SCN, but not other groups, have annual bone marrow examinations with chromosome analysis to recognize evolution to MDS/AML as early as possible. One established marker of transition is the development of mutations in the receptor for G-CSF, but time from the first appearance of such a mutation to clinical signs of MDS/AML can be very long even many years.[35]

Chromosomal changes such as monosomy 7 are a more specific finding. Ongoing research suggests that other markers, i.e. *RUNX1* mutations, may occur later and be a better predictor of developing AML.[36]

In patients with mild or asymptomatic neutropenia, the bone marrow reserve pool of mature neutrophils can be assessed less invasively by a glucocorticoid stimulation test.[37] After a baseline CBC with differential count, prednisone 1–2 mg/kg is administered as a single oral dose and the CBC/differential repeated 4–6 hours later. A more than two-fold rise indicates the presence of an adequate bone marrow reserve pool that can be mobilized at times of stress or infection. This condition is sometimes termed, nonspecifically, "chronic benign neutropenia."

Neutrophil antibodies and antigens—Testing for anti-neutrophil antibodies, by immunofluorescence, agglutination, or flow cytometric assays, may help support the diagnosis of autoimmune neutropenia, but must be interpreted in the context of clinical and bone marrow findings, as the tests are fraught with false positive and false negative results.[14;38;39] Testing should only be performed by a laboratory with considerable experience in performing and interpreting the assay. Determination of parental neutrophil antigens may be helpful for the diagnosis of neonatal alloimmune neutropenia.[40]

Genetic testing—Identification of the specific gene and mutation responsible for congenital neutropenia may help support the diagnosis, indicate a relative risk for late complications such as MDS/AML or aplasia (e.g. in SCN or dyskeratosis congenita), guide screening for non-hematological phenotypes (e.g. in Shwachman-Diamond syndrome or G6PC3 defects), and provide a basis for genetic counseling of the family. However, genetic testing may be expensive and have unanticipated psychological and social consequences, and may fail to identify a mutation in many patients.

Other laboratory tests that may aid in the diagnosis of chronic neutropenia include evaluations for nutritional deficiencies (e.g. vitamin B12, folate, copper), immune deficiencies (e.g. quantitative immunoglobulins), and rheumatologic disorders (e.g. anti-nuclear antibody and other tests). Based on clinical findings and family history, testing for phenotypic or genotypic findings of specific neutropenic syndromes (Table 2) may be indicated, often in consultation with a geneticist.

Laboratory testing in transient neutropenia should be directed at underlying diseases, particularly treatable infectious agents such as bacteria, protozoa, and HIV.

Management of Isolated Neutropenia

Acute infections

Fever in the setting of profound neutropenia is a medical emergency requiring immediate treatment with broad spectrum antibiotics. Patients with ANC of 0.2×10^9/L or less almost invariably require hospital admission for IV antibiotics, with the choice of drugs depending upon local community and/or hospital flora and antibiotic sensitivities. Importantly, antibiotic therapy should include anaerobic coverage when fever is accompanied by abdominal pain, as may recur frequently in cyclic neutropenia. Patients with an ANC 0.2×10^9/L usually require admission, but culturing and out-patient antibiotics may be used for some with more benign forms of neutropenia, such as chronic autoimmune neutropenia of infancy, with relatively good delivery of neutrophils to tissues sites of infection.

Chronic Neutropenia

Individuals with the diagnosis of chronic neutropenia who maintain ANC>1.0 × 10^9/L on G-CSF therapy may be evaluated and treated as would any non-neutropenic patients. Those in the intermediate range of ANC 0.5–1.0 × 10^9/L need evaluation on a case-by-case basis.

Precautions to Avoid infections

Although many families try to sterilize their living quarters with disinfectants, simple soap-and-water hygiene and hand-washing, plus a few common-sense precautions are sufficient. In fact, most measures are not only inconvenient but ineffective, because the source of most infections in neutropenic patients are their own skin and gut flora. Although neutropenia does not impair defense against viral infections, avoidance of very crowded areas or close contact with infected individuals may decrease the likelihood of a precautionary admission for febrile neutropenia or for virus-induced mucosal breach to provide entry for a secondary bacterial infection. To avoid invasive fungal infection, neutropenic patients should also avoid highly contaminated sources such as mulch, dusty construction or demolition sites, and bird or animal waste. Good dental hygiene is also important, to minimize chronic gingivitis and tooth loss.

Myeloid Growth Factor Therapy

Hematopoiesis is regulated by a family of hematopoietic growth factors; the myeloid-specific cytokine granulocyte colony-stimulating factor (G-CSF) is the principal regulator of the blood neutrophil count. Recombinant human G-CSF (filgrastim; Neupogen®, Amgen, Inc., Thousand Oaks, CA) is now widely used to stimulate neutrophil production in patients with chemotherapy-induced neutropenia. It is also very useful for management of severe chronic neutropenia, with slightly different principles governing its administration.

Randomized controlled trials established that patients with congenital, cyclic and idiopathic neutropenia have fewer mouth ulcers, febrile events and infections when treated with daily, subcutaneous G-CSF.[11;41] In the original trials G-CSF was given with careful adjustment of the daily dose to increase counts to the low-normal range, i.e., to raise counts to approximately 2 × 10^9/L. Subsequently, in work overseen by the Severe Chronic Neutropenia International Registry (SCNIR), it has been learned that a G-CSF dose sufficient to maintain blood neutrophils greater than approximately 1.0 × 10^9/L is sufficient for many patients. G-CSF can be administered every other day or three days per week for many patients, particularly those with idiopathic, autoimmune, or cyclic neutropenia. In contrast to patients receiving G-CSF after chemotherapy, is very important to give the lowest effective dose of G-CSF. Ordinarily it is easier to start with a very low dose, 0.5 to 3 mcg per kilogram per day given on a daily basis, going up gradually to find the lowest effective dose and then giving the injections less often. Both children and adults respond well to G-CSF and adverse events are relatively infrequent. The most common acute adverse events associated with G-CSF therapy are bone pain and headache. Less frequent administration of larger doses can intensify bone pain, so weekly or twice weekly injections are seldom tolerated, and increasing the frequency of administration may ameliorate pain in some patients. Injection site reactions, fever, chills and other acute inflammatory responses are quite uncommon. G-CSF has now been administered to many patients with severe chronic neutropenia on a daily or alternate day basis for more than 10 years. Treatment responses tend to be quite stable once an effective dose for the individual patient is found. The dose should be gradually adjusted for body weight in growing children, with monitoring of the response.

From the beginning of long-term use of G-CSF to treat chronic neutropenia, there have been concerns that this growth factor might stimulate development of leukemia. Before G-CSF

was available it was known that patients with SCN are at risk of developing AML. For this reason the SCNIR was established to determine the risk of AML during long-term G-CSF therapy. This observational study has established that patients with severe congenital neutropenia who respond poorly, i.e., requiring more than the median dose of 8 mcg/kg/day, have a greater risk of AML than patients responding to lower doses.[42;43] Patients with cyclic, idiopathic and autoimmune neutropenia, appeared to have virtually no risk of evolving to develop MDS or AML on long-term G-CSF treatment.[42] Recent studies also suggest that some ELANE mutations are associated with a higher development of MDS/AML than others.[23;44] Currently most experts believe that the risk of MDS/AML is largely intrinsic and related to the underlying specific genetic cause of neutropenia, but it is difficult, if not impossible, to rule out G-CSF as a contributing risk factor for development of AML in these patients.

It is important to keep in mind that the major objective of G-CSF therapy is to provide a normal life style, and patients with corrected ANCs on G-CSF therapy do not need to pursue any precautions beyond those practiced by their normal peers. It is also important to treat only patients with a clinical history of infections and problems with oral health sufficient to justify regular and expensive, long-term injection therapy. An individual patient can be evaluated by a brief clinical trial to determine the response to G-CSF and the benefits of treatment; ordinarily only about 4 to 6 weeks are sufficient to make this assessment. In patients with neutropenia responding to G-CSF, discontinuation of this therapy leads to return of neutrophil levels to their baseline, usually within a few days

Alternatives to G-CSF Treatment

There are no other hematopoietic growth factors, including GM-CSF, which are of proven efficacy for long-term treatment of chronic neutropenia. For many years corticosteroids were used. These agents may increase counts modestly but do not stimulate neutrophil production and carry the added risk of increasing the patient's susceptibility to infection, as well as multiple additional toxicities. Lithium salts, androgens and vitamin therapies are also not of proven benefit. Pegylated G-CSF has now been used in many patients; most respond but some respond excessively with marked leukocytosis, bone pain, and even, rarely, infiltration of the tissues by neutrophils.[45;46] Neutrophil transfusions are a potential therapy for acute neutropenia but are not suitable as a long term approach to management because of the likelihood of allo-immunization and severe transfusion reactions.

Hematopoietic stem cell transplantation is an alternate therapy which can be used in patients failing to respond to G-CSF (i.e., requiring > 20 mcg/kg/day, an inconvenient dose to try to administer on a long term basis) or with high risk of evolving into MDS/AML (e.g. requirement for high doses of G-CSF or presence of abnormal cytogenetic clones in the bone marrow). Transplantation, with or without pre-transplant chemotherapy, also is used as part of the treatment strategy for patients with frank MDS or AML. At present there is no clear consensus about the frequency and specific markers to use as indicators for hematopoietic transplantation. Success of a transplant also depends upon the availability and quality of the match of the potential donor and the recipient. Consultation with an expert in hematopoietic stem cell transplantation is highly recommended for patients not responding well to G-CSF, developing cytopenias while on G-CSF, or developing chromosomal changes or increasing myeloblasts in the marrow.

Supportive care

Chronic periodontal disease is a hallmark of untreated or refractory neutropenia. Good dental hygiene and regular professional treatment are necessary to forestall or prevent tooth loss, and far outweigh any theoretical risk of bacteremia from local trauma. Psychosocial

support can help alleviate the psychological and financial burdens of a chronic illness, and can be provided both by health professionals and by patient/parent groups such as the National Neutropenia Network in the U.S. (http://www.neutropenianet.org/) and the Neutropenia Support Association, Inc., in Canada (http://www.neutropenia.ca/).

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Abbreviations

AML	acute myeloid leukemia
ANC	absolute neutrophil count
CyN	cyclic neutropenia
G-CSF	granulocyte colony-stimulating factor
LGL	large granular lymphocyte
MDS	myelodysplastic syndrome
SCN	severe congenital neutropenia

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Table 1

Causes of transient neutropenia

INFECTION	
Viral	Cytomegalovirus, Epstein-Barr virus, HIV, influenza, parvovirus B19
Bacterial	Brucella, paratyphoid, tuberculosis, tularemia, typhoid; *Anaplasma phagocytophilum* and other rickettsia
Protozoan	*Plasmodium vivax, P. falciparum*
DRUGS	
Anticonvulsant	Carbamazepine, valproate
Antimicrobial	Sulfonamides, penicillins, trimethoprim/sulfamethoxazole
Antipsychotic	Clozapine, olanzapine, phenothiazines
Antirheumatic	Gold, levamisole, penicillamine
Antithyroid	Methimazole, propylthiouracil
Other	Aminopyrine, deferiprone, rituximab, levamisole-adulterated cocaine
IMMUNE	
Neonatal isoimmune	
Autoimmune	

Table 2

Causes of chronic neutropenia

EXTRINSIC	
Nutritional	Vitamin B12, folate, copper, protein-calorie
Immune	Autoimmune
	Congenital immunological disorder
	Systemic autoimmune disorder
INTRINSIC	
Myelodysplasia	
Acquired bone marrow failure	Aplastic anemia
Congenital bone marrow failure	
Isolated neutropenia	Severe congenital neutropenia Cyclic neutropenia
Neutropenic syndromes	Disorders of granule sorting: Chédiak-Higashi syndrome, Cohen syndrome, Griscelli syndrome type 2, Hermansky-Pudlak syndrome type 2, and p14 deficiency
	Disorders of metabolism: Glycogen storage disease type 1b, Barth syndrome, Pearson syndrome
	Disorders of immune function: Hyper-IgM syndrome, WHIM syndrome, cartilage-hair hypoplasia, Schimke immuno-osseous dysplasia
	Disorders of molecular homeostasis: Dyskeratosis congenita, Fanconi anemia, Shwachman- Diamond syndrome
Idiopathic	