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REVIEW ARTICLE

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How I investigate neutropenia

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Abstract

Neutropenia is a common laboratory finding in adults and children. Its underlying causes are extremely heterogeneous and include benign conditions, autoimmune disorders, infections, and malignancies. The clinical laboratory plays a central role in the diagnosis of these disorders, including data derived from hematology, microbiology, molecular biology/cytogenetics, and clinical chemistry. The purpose of this review is to (a) highlight the clinical, hematologic, and molecular genetic features of the major entities resulting in neutropenia and (b) outline an algorithm-based approach to permit the classification of neutropenias.

KEYWORDS
neutropenia, neutrophils

1 | HOW ARE NEUTROPHILS ENUMERATED, AND WHAT IS NEUTROPENIA?

The enumeration of neutrophils is a routine function of commercially available hematology instrumentation platforms. This is achieved using a combination of impedance volume/conductivity and five-angle light scatter (Beckman Coulter); fluorescent staining, forward/side scatter, and side fluorescent light detection (Sysmex); multiangle polarized scatter separation and three-color fluorescence detection (Abbott); and peroxidase staining, light scatter, and absorption (Siemens). All methods have been demonstrated to have an acceptable correlation with the reference method, a visual differential count of a well-prepared peripheral blood smear.[1]

In most laboratories, the absolute neutrophil count (ANC) of normal adults ranges from 1.5 to 7.0 × 10^9/L. Although some laboratories, especially those serving a predominantly pediatric population, use published reference ranges, the optimal approach for the laboratory is to develop its own reference ranges for all hematologic parameters including absolute neutrophil count (ANC). This is because the lower limit of the ANC can vary depending on the age and race of the patient. In normal neonates and infants, the lower limit of normal is ~2.5 × 10^9/L. In older children and adults, it decreases to ~1.5 × 10^9/L. In up to ~25% of African American children/adults, the absolute neutrophil count ranges from 1.0 to 1.5 × 10^9/L. For these reasons, it is important to be aware of the age and ethnicity-related differences in the ANC, to avoid unnecessary testing.[2,3]

Although the ANC is generally reliable, there are preanalytic phase issues that rarely result in an erroneous result. An example of this is pseudoneutropenia due to in vitro leukocyte aggregation, which may occur in the presence of antibodies to ethylenediaminetetraacetic acid or cold agglutinins. In such cases, review of the peripheral blood smear and/or repeat complete blood count (CBC) identifies a normal number of circulating neutrophils.[4-6]

2 | HOW IS NEUTROPENIA CLASSIFIED?

Using the above criteria, most laboratories would define neutropenia in infants with an ANC < 2.5 × 10^9/L and in adults with an absolute neutrophil count < 1.5 × 10^9/L.

The differential diagnosis of causes of neutropenia has been conceptualized by a number of different ways. The simplest of these subclassifies neutropenia on the basis of an absolute count into three groups: mild (ANC 1.0-1.5 × 10^9/L), moderate (ANC 0.5-0.999 × 10^9/L), and severe (ANC < 0.5 × 10^9/L), the last group at the greatest risk for infection. A second classification system recognizes that the causes of neutropenia are varied and can be broadly grouped into neoplastic and nonneoplastic causes. In cases of neutropenia of neoplastic origin, clues about the specific etiology can

be gathered from the presence of abnormalities in other lineages. Patients with neutropenia of nonneoplastic origin often have isolated neutropenia which is most often of constitutional or acquired origin. A third classification system recognizes that the causes of neutropenia vary depending on patient age (Table 1).

Although all these systems are valid, a classification system recognizing the basic physiology of granulocyte maturation in the bone marrow (BM) and the fate of terminally differentiated neutrophils in the blood and other end organs is particularly useful to laboratorians who also are involved in the morphologic review of BM biopsy materials, and will be the system used in this review.

In order to understand the rationale for this classification, it is necessary to have a basic overview of the features of normal granulocyte maturation. Briefly, neutrophils are derived from BM stem cells, which undergo proliferation and differentiation in the BM. The neutrophils are released into the blood where they have a survival time of ~5-135 hours. It is important to note the circulating neutrophils represent only ~5% of the total number of neutrophils in the body. The remaining 95% of neutrophils are present as maturing granulocytes in the BM and the storage pool, which is defined as a body of mature neutrophils held by the body in reserve in the marrow. Neutropenia, then, can be a result of failure of any step in this process. Neutropenia due to a defect involving the stem cell/maturing granulocyte/storage pool phases is classified as neutropenia with decreased BM reserve, which is subclassified as primary (ie, due to a defect in granulopoiesis) or secondary (due to a condition with suppresses normal granulopoiesis). Neutropenia due to a defect involving the neutrophils after they exit the BM is classified as neutropenia with normal marrow reserve. A detailed discussion of the mechanisms of neutropenia with examples of specific disorders is as follows.

TABLE 1 Age-related causes of neutropenia

Neonate
Infection—by far the most common cause
Maternal hypertension and/or drug treatment
Maternal antibody production
Constitutional disorders, eg, cyclic neutropenia, Kostmann syndrome, Chediak-Higashi syndrome
Infant/child
Infection—common
Autoimmune neutropenia
Neoplasms replacing the BM
Idiosyncratic drug reactions
Secondary autoimmune neutropenia in collagen vascular disorders
Immunodeficiency disorders
Myeloablative therapies
Constitutional neutropenia disorders—rare
Megaloblastic anemia—rare
Copper deficiency—rare
Adult
Idiosyncratic drug reactions—most common cause in ambulatory patients
Infections—common
Neoplasms replacing the BM—common
Myeloablative therapies—common
Secondary autoimmune neutropenia in collagen vascular disorders
Autoimmune disorders including white blood cell aplasia

3 | PRIMARY CAUSES OF NEUTROPENIA WITH DECREASED BM RESERVE

3.1 | Severe congenital neutropenia/Kostmann syndrome

Severe congenital neutropenia (SCN) is a rare cause of neutropenia, identified in ~1-2 patients per 1 000 000 live births (Table 2).[7] The reported patterns of inheritance are variable and include autosomal dominant (AD), autosomal recessive (AR), and X-linked. Some cases are sporadic in origin. The term Kostmann syndrome is recommended to be used only for cases with the AR form of inheritance. Mutations in the neutrophil elastase-2 (*ELA-2*) gene have been identified in a majority of tested cases, resulting in apoptosis of precursor cells.[8] In some cases, the mutational events lie in genes that mediate repression of transcription of myeloid genes, including *GF11*, *PRDM5*, and *PFAAP5*. The result of these mutations is severe neutropenia from birth, with an ANC < 0.5×10^9/L. Patients are at an increased risk for development of hematologic malignancy; ~2% of affected individuals per year progress to myelodysplastic syndrome or acute myeloid leukemia. BM evaluation reveals a maturation arrest at the promyelocyte/myelocyte stage. Symptomatic treatment for SCN includes granulocyte-colony stimulating factor (G-CSF), although hematopoietic stem cell transplant is indicated, in particular for patients with poor neutrophil response to high dose G-CSF, which is associated with increased risk of malignancy.[9]

3.2 | Shwachman-Diamond syndrome

Shwachman-Diamond syndrome (SDS) is an extremely rare cause of severe neutropenia (ANC < 0.5×10^9/L), accompanied by metaphyseal dysplasia and exocrine pancreas deficiency. It can be inherited in an AR pattern, although sporadic cases occur. In 90% of cases, mutations involving the Shwachman-Bodian-Diamond syndrome gene, located in the centromeric region of chromosome 7, are identified.[10,11] The syndrome does not appear to be associated with elastase mutations. Neutropenia in SDS appears to be related to FAS-mediated neutrophil precursor apoptosis and is more severe in patients with shortened telomere length, increased expression of p53 protein, and increased myeloid cell apoptosis.[12,13] As with SCN, there is an increased risk of hematologic malignancy in SDS, so routine CBCs ~ 3-4 times per year are recommended, with BM indicated for patients with increasing cytopenias. Cytogenetic analysis of the BM may be useful, since identification of the isochromosome *i(7p)* is especially associated with development of myelodysplastic syndrome in these patients.[14]

TABLE 2 Neutropenia with decreased BM reserve (adapted and updated by the author from Ref. [7]. For details, see text

	Disorder	Mechanism	Inheritance/ frequency	Clinical characteristics	Diagnostic
Primary	Severe congenital neutropenia	Apoptosis of precursor cells; *ELA-2* mutations	AR, AD, S; 1-2/million	Severe neutropenia in newborn	BM—promyelocyte/myelocyte arrest
	Shwachman-Diamond syndrome	Abnormal BM stroma; FAS-mediated granulocyte apoptosis; *SBDS* mutations	AR, S; Extremely rare	Infections; steatorrhea; exocrine pancreas deficiency; ~33% progress to MDS/AML	Hypoplastic BM; normal sweat chloride; increased fecal fat; short stature
	Cyclic neutropenia	Precursor apoptosis; some cases with *ELA-2*(*ELANE*) mutations	AD, S; 1-2/ million	Recurrent fevers every 21 days; skin and otolaryngeal infections	CBC 2-3 times per week for 8 weeks
Secondary	Large granular lymphocytic leukemia and related disorders	Increased apoptosis due to FAS ligand	Uncommon	Recurrent fever; mouth ulcers; splenomegaly; arthritis; primarily adults	Clonal proliferation of lymphocytes; CD3 ± with CD8 + or CD16/CD56, or CD57
	Chemotherapy	Direct toxicity to neutrophil precursors	Common	Severity of neutropenia depending on agent; high risk of infection	BM biopsy indicted when neutropenia is unusually prolonged or severe
	Drug-induced (nonimmune)	Direct suppression of myelopoiesis	Not uncommon	Comprises ~ 70% of cases of neutropenia; fatal in up to 25% of cases	Clinical history; empirical discontinuation of drug
	Nutritional	Ineffective myelopoiesis	Uncommon	Protein-calorie malnutrition; folate/B12/ copper deficiency	Clinical history; BM biopsy if necessary
	Viral infection (most commonly EDBV, measles, CMV, hepatitis, HIV)	Direct effect or immune-mediated	Uncommon	Degree of neutropenia variable	Clinical history; viral studies if necessary

Note: See text for a more detailed discussion.

3.3 | Cyclic neutropenia

Cyclic neutropenia (CN) is a periodic form of severe neutropenia (ANC 200/mm^3) occurring in regular intervals every ~21 days (range ~12-31 days). The neutropenia has a duration of ~3-5 days. Though fatal infections are uncommon, recurrent fever and oropharyngeal/skin infections are common.[15] An AD pattern of inheritance has been described, although sporadic cases do occur. Nearly all tested patients have *ELA-2* gene mutations. In addition to genetic testing, serial CBC analyses are used to identify a recurrent pattern of neutropenia. BM biopsy is usually not indicated. Most patients respond to G-CSF, and there is no increased risk of hematologic malignancy.[16]

3.4 | Chédiak-Higashi syndrome and other causes of primary neutropenia with decreased BM reserve

Chédiak-Higashi syndrome (CHS) is an AR-inherited disorder with decreased phagocytosis, recurrent pyogenic infections, and oculocutaneous albinism caused by a mutation in lysosomal trafficking regulator protein. The mutational event is related to mutations in the *LYST* gene on chromosome 1q43. The result is a mild neutropenia with increased risk of infection due to decreased microbicidal activity.[19,20]

There are many other congenital conditions associated with neutropenia. In these conditions, the degree of neutropenia is often mild and is not universally identified in all cases. These include myelokathexis/neutropenia with tetraploid nuclei,[17] reticular dysgenesis,[18] and dyskeratosis congenita.[14]

4 | SECONDARY CAUSES OF NEUTROPENIA WITH DECREASED BM RESERVE

4.1 | T cell large granular lymphocytic leukemia and related disorders

A detailed discussion of LGLL is beyond the scope of this review. T cell large granular lymphocytic leukemia (T-LGL) is reviewed in further detail elsewhere in the Education Supplement.

T-LGL is defined by a peripheral blood lymphocytosis of >6-month duration. The malignant cells are small with variable amounts of cytoplasm with innumerable fine or coarse azurophilic granules.[21] T-LGL most commonly affects middle-aged or elderly individuals and has an indolent clinical course. The disease course is typically indolent and is often detected incidentally during a medical workup for an unrelated disorder. The CBC is abnormal: Patients have a peripheral lymphocytosis with an absolute count of large granular lymphocytes >2 × 10^9/L or with large granular lymphocytes comprising >80% of total lymphocytes. Many patients have an associated neutropenia. Many patients present with a variable degree of splenomegaly (Figure 1).[22,23]

The usual immunophenotype is CD2+/CD3+/CD8+/CD57+. Many cases demonstrate decreased expression or absence of the common T cell antigens CD5 and/or CD7. Cases demonstrating expression of CD56 are generally classified as natural killer cell neoplasms, although they may have similar clinical features.[24-26]

The differential diagnosis includes disorders with benign polyclonal or oligoclonal expansions of large granular lymphocytes such as the postallogeneic BM transplant state, low-grade B cell malignancies, human immunodeficiency virus (HIV) infection, common variable immune deficiency, and rheumatoid arthritis.[27]

At initial presentation, T cell receptor gene rearrangement studies and/or flow cytometric Vβ analysis can be performed to assess to proliferation for monoclonality, generally on a peripheral blood specimen. Reassessment can be performed at least 6 months later. If the peripheral lymphocytosis persists, a new blood specimen can be analyzed. Identification of a clonal population in both specimens, in the presence of the other criteria, can confirm the diagnosis. In some specialized centers, flow cytometric analysis of killer cell immunoglobulin-like receptor (KIR) family members can be useful to establish the diagnosis. A restricted range of KIR expression by the lymphocytes in a specimen is considered indicative of clonality.[28]

Neutropenia in T-LGL is common, occurring in up to 80% of individuals, and is the most common indication for treatment in patients with T-LGL. Interestingly, the degree of neutropenia does not appear to correlate with susceptibility to infection, since many patients can have protracted neutropenia with no associated complications.[29]

4.2 | Chemotherapy

Neutropenia is a common complication of systemic chemotherapy due to direct toxicity to neutrophil precursors in the BM. The severity of neutropenia is dependent on treatment intensity and regimen.[30] In patients with a poor marrow reserve, there is a high risk of infection. In most cases, the cause of the neutropenia is obvious and no directed workup is necessary. However, in situations when neutropenia unusually prolonged or severe, BM biopsy may be indicated. Treatment is generally supportive. In select situations, treatment with G-CSF may be necessary.[31,32]

4.3 | Drug-induced neutropenia (nonimmune)

There are two mechanisms of drug-induced neutropenia: immune-related (discussed below) and nonimmune-related. Cell lineages with high turnover, such as granulocyte precursors, may be prominently affected and are directly suppressed. This is a significant cause of neutropenia in ambulatory patients; medications are believed to account for ~ 70% of all cases of neutropenia, with mortality rates as high as 12%-25%. Drugs such as phenothiazines, antithyroid medications, and chloramphenicol have been implicated. Neutropenia may improve spontaneously once the drug is discontinued, although G-CSF treatment may be indicated.[33,34]

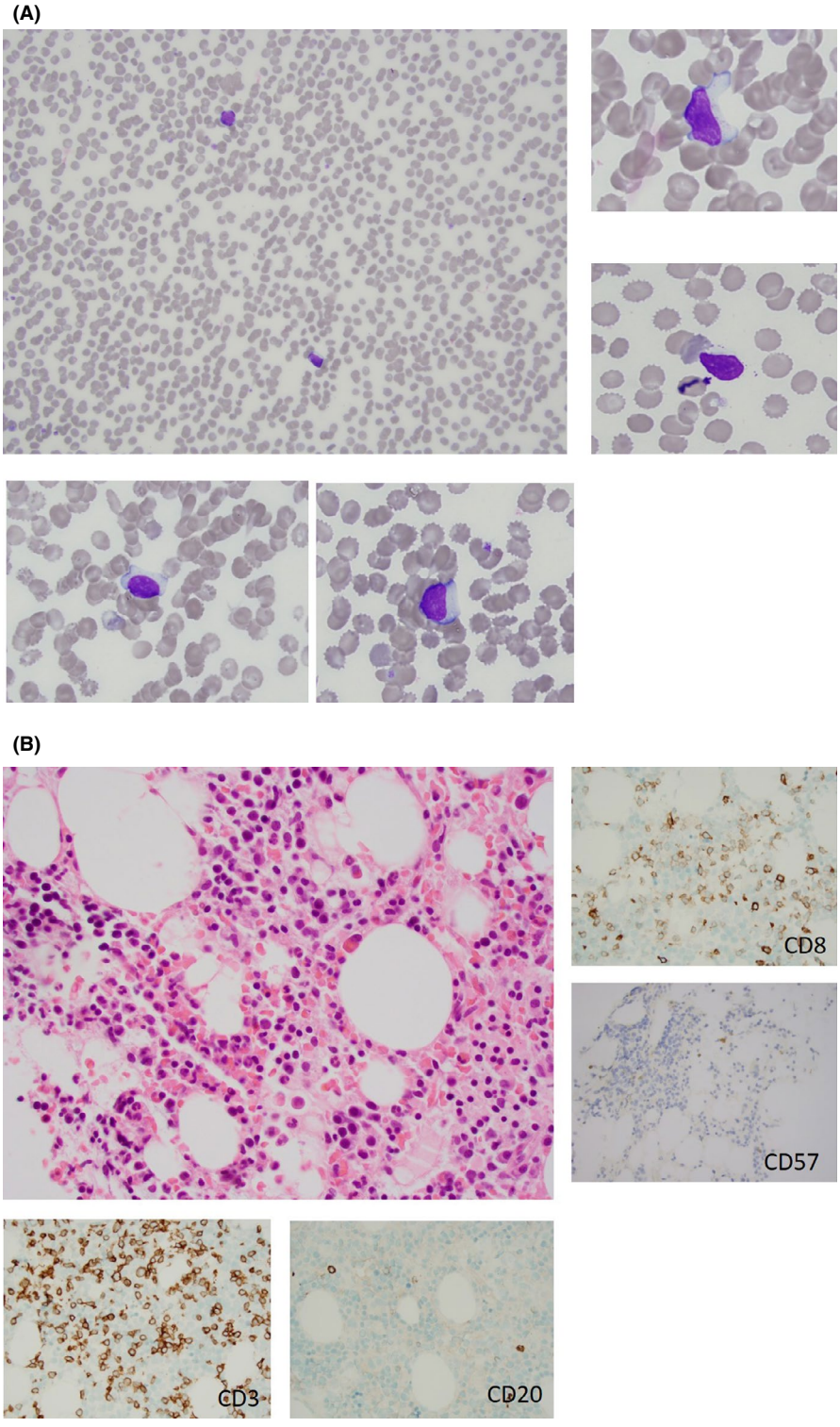

FIGURE 1 Adult patient with T cell large granular lymphocytic leukemia and neutropenia: (A) peripheral blood smear demonstrating neutropenia and increase circulating large granular lymphocytes (Wright–Giemsa, original magnification x1000) and (B) BM core biopsy showing a subtle infiltration by a proliferation of lymphocytes with the following immunophenotype: CD3+/ CD4-/CD8+/ CD56-/CD57- (Wright–Giemsa [aspirate], and hematoxylin and eosin [biopsy] original magnification x1000)

4.4 | Nutritional deficiency

A variety of macro- and micronutrient deficiencies may result in peripheral cytopenias, including neutropenia, as a result of ineffective myelopoiesis. Protein-calorie malnutrition (including anorexia nervosa) in its most severe form can cause a BM failure picture with marked BM hypoplasia. Folate/vitamin B12 deficiency and copper deficiency often have an associated neutropenia, the severity of which is variable (Figure 2).[35] Most often, the folate/B12 and copper-deficient patients have an accompanying megaloblastic anemia and mild thrombocytopenia, which are important diagnostic clues. Diagnosis may be confirmed with appropriate clinical laboratory workup. BM biopsy is generally not necessary. Treatment consists of supportive care with correction of nutrition and the vitamin deficiency.[36]

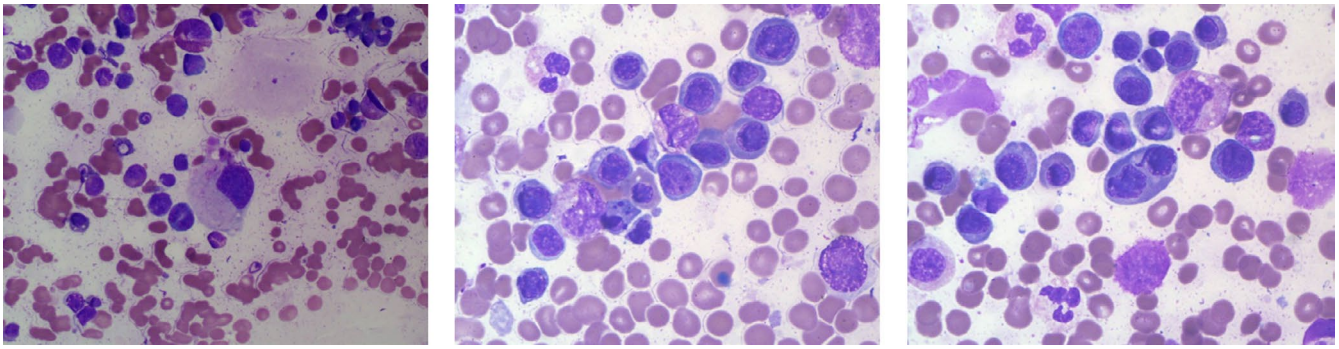

FIGURE 2 Megaloblastic anemia in 16-year-old girl with vitamin B-12/folate deficiency and pancytopenia. BM aspirate demonstrating pronounced dyspoietic changes in the erythroid lineage and decreased granulocytic elements (Wright–Giemsa, original magnification x1000)

4.5 | Viral infection (varicella, EBV, measles, CMV, hepatitis, HIV)

Viral infection can suppress BM granulopoiesis either directly or via an immune-mediated process. The degree of neutropenia is highly variable, ranging from mild to severe. HIV-associated neutropenia may be particularly symptomatic and associated with aspergillosis and pyomyositis. In patients with severe neutropenia and infection, treatment may include granulocyte-colony stimulating factor (G-CSF).[37]

5 | NEUTROPENIA WITH NORMAL MARROW RESERVE

5.1 | Chronic benign neutropenia of infancy and childhood

As its name implies, chronic benign neutropenia of infancy and childhood is generally detected incidentally in children less than 14 months of age, with a median age of detection of 8 months (Table 3).[7] Patients present with a marked neutropenia with an ANC < 500/mm^3. This is one of the more common causes of neutropenia in this age group and appears to be due to an antineutrophil antibody. Although not generally indicated, when a BM biopsy is performed, there are normal to slightly increased numbers of myeloid precursors. Treatment is generally supportive in nature. Despite the low ANC, the risk of infection is not high.[38,39]

5.2 | Nonimmune chronic benign neutropenia

Nonimmune chronic benign neutropenia (NCBN) has been described primarily in adults. This uncommon cause of neutropenia is generally detected as an incidental finding on CBC. The degree of neutropenia is mild (ANC > 800-1000/mm^3) and appears to be due to increased apoptosis of neutrophils. Treatment is generally supportive. There is minimal risk of infection.[40]

5.3 | Ethnic or benign familial neutropenia

Ethnic or benign familial neutropenia (EN) is a clinically benign cause of neutropenia. As its name suggests, it occurs predominantly in specific ethnic groups such as American and South African Blacks, Yemenite, Black Bedouins, and Falasha Jews, where it is inherited in an AD fashion. The cause of the neutropenia is unknown in most cases. It is generally incidentally detected, and there is no increased risk of infection. Diagnosis is made following exclusion of clinically significant causes of neutropenia in individuals from affected groups. Because it is clinically benign, there is no treatment indicated. It is important for clinical laboratories serving populations with EN to be aware of this disorder in order to avoid unnecessary testing and treatment.[3]

5.4 | Autoimmune neutropenia

Autoimmune neutropenia may develop spontaneously, although it is also associated with immune thrombocytopenia purpura, immune hemolytic anemia, systemic lupus erythematosus, and Felty syndrome. The neutropenia is caused by antibody-mediated destruction although splenic sequestration can also occur.BM biopsy reveals increased marrow cellularity with late maturation arrest. Therapy is based on identifying and treating the primary autoimmune disorder. In patients who develop decreased BM granulocyte reserves, G-CSF is indicated.[41]

5.5 | Alloimmune neutropenia

Maternal alloimmunization is a potential cause of neutropenia in newborns. Neutrophil-specific antibodies HNA-1a/1b/2a are identified in 50% of cases. Other antibodies implicated in some cases include HNA-1c, HNA-3a, and HNA-4a. The degree of neutropenia is generally moderate to severe. It is generally identified shortly after birth and spontaneously resolves by 2-3 months of age. There is an increased risk of infection in affected infants, manifesting as skin

TABLE 3 Neutropenia with normal BM reserve (adapted and updated from Ref [7])

Disorder	Mechanism	Inheritance/frequency	Clinical characteristics	Diagnostic
Chronic benign neutropenia of infancy and childhood	Antineutrophil antibody	Common	90% detected before 14 mo of age; ANC usually < 500/mm^3; no risk of infection	BM—normal/increased myeloid elements
Nonimmune chronic benign neutropenia	Increased apoptosis	Not uncommon	Adults; incidental detection on CBC; ANC > 800-1000/mm^3	BM—hypoplasia of myeloid series
Ethnic or benign familial neutropenia	Unknown	AD Not uncommon	ANC 800-1400/mm3; no risk of infection; African Americans; Yemenite; Bedouins; Falasha Jews	Diagnosis of exclusion; similar findings in family member(s)
Autoimmune neutropenia	Antibody-related destruction; sequestration	Not uncommon	Associated with ITP, immune hemolytic anemia, SLE, Felty syndrome	BM—increased cellularity; (late) maturational arrest
Alloimmune neutropenia	Maternal alloimmunization	Not uncommon	Moderate/severe neutropenia in newborn; increased cutaneous infections	Resolves by 3-4 months of age
Drug-induced neutropenia	Antibody- or complement-mediated	3.4/million	Fever, sepsis, pneumonia; up to 25% mortality; 80% recover	Medication history; BM—late maturational arrest
Infection-related neutropenia	Virus-mediated antibody	Common	Clinical history of infection	Parvovirus B19 and HIV testing if indicated
Hypersplenism	Sequestration; destruction	Not uncommon	Mild neutropenia; associations—infection (malaria, TB), neoplasm, collagen vascular disease, hemolytic anemia	Peripheral blood smear-spherocytic red blood cells

Note: See text for a more detailed discussion.

infections, omphalitis, fever, and respiratory/urinary tract infection. It is responsible for ~ 1.5% of admissions to the neonatal intensive care unit and may have a morality rate as high as 5%. Treatment is generally supportive. G-CSF is indicated in septic patients.[42]

5.6 | Drug-induced neutropenia (antibody-mediated)

Drug-induced neutropenia via antibody- or complement-mediated mechanisms is uncommon, with an estimated frequency of 3.4 cases per million individuals. Patients often present with fever, sore throat, sepsis, stomatitis, and pneumonia. As with nonimmune-mediated drug-induced neutropenia, the mortality rate is relatively high. BM biopsy may demonstrate a late maturation arrest in granulocytes. Treatment consists of discontinuing the offending drug. Splenectomy is rarely indicated, generally in patients with pronounced anemia and thrombocytopenia.

5.7 | Infection-related neutropenia (antibody-mediated)

Postinfectious antibody-mediated neutropenia is common and may be related to bacterial or viral infection. The diagnosis is established based on the clinical history of infection and confirmatory microbiologic workup. BM findings are variable and may demonstrate decreased marrow reserve, in particular in patients with bacterial sepsis. Therapy is generally directed at treating the underlying infection. In situations when a maturation arrest is identified in the BM specimen, G-CSF may be indicated (Figure 3).

5.8 | Hypersplenism

Neutropenia, generally mild, may be identified in patients with hypersplenism (Figure 4). Hypersplenism is associated with a variety of diseases, including infection (classically malaria, and tuberculosis), a variety of neoplasms, collagen vascular disease, liver disease, and hemolytic anemia. The mechanism of neutropenia is related to sequestration of neutrophils within the spleen, with possible destruction of the cells. The degree of cytopenias appears to be unrelated to spleen size. Diagnostic is based on clinical examination and radiography demonstrating splenic enlargement. The ANC may improve after treating the underlying disorder. Splenectomy is reserved for rare cases with intractable anemia and/or thrombocytopenia accompanying the neutropenia.[43]

5.9 | Maternal hypertension

Maternal hypertension may be a cause of low ANC in newborns. Approximately 50% of neonates born to women with pregnancy-induced hypertension will experience neutropenia, which is generally transient and spontaneously corrects ~30 days of birth. Intrauterine growth retardation, premature rupture of membranes, and HELLP (hemolysis, elevated liver enzymes, and a low platelet count) syndrome are at particular risk of neutropenia.[44] The neutropenia, though self-limited, may be clinically significant as there is an increased risk of nosocomial infection.[45]

6 | THE DIAGNOSTIC APPROACH TO NEUTROPENIA

The diagnostic approach to neutropenia should take into account the broad differential diagnosis and the appropriate sequence of clinical laboratory testing best tailored to lead to a correct conclusion in a timely and cost-effective manner. Laboratorians should be prepared to perform a rational sequence of laboratory tests and also recommend the best testing strategies to the treating physician. Prior to any laboratory testing, a detailed clinical history and thorough physical examination is recommended. In select patients, radiographic findings may be important.

The clinical laboratory provides invaluable input, including:

- (Serial) CBCs;
- Morphologic review of peripheral blood smear;
- Testing directed to immune status, collagen vascular disorders, viral infection; and
- BM biopsy (particularly in adults with new-onset neutropenia, children with suspected neoplasms, aplasia, BM infection, etc)

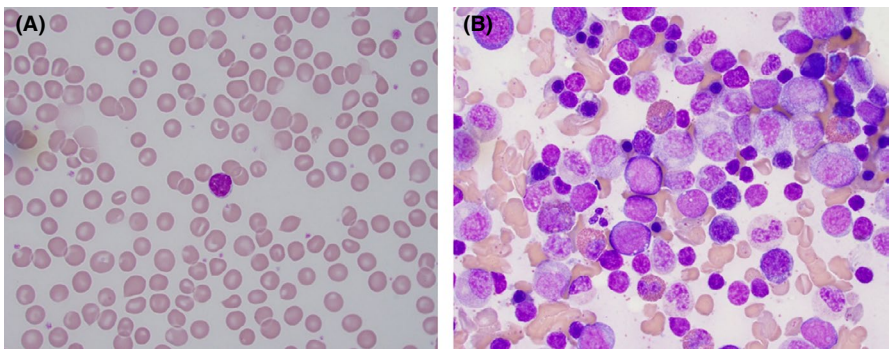

FIGURE 3 Infection-related neutropenia in a 3-year-old girl: (A) peripheral blood smear demonstrating neutropenia and (B) BM aspirate smear demonstrating maturation arrest in myeloid lineage (Wright–Giemsa, original magnification x1000)

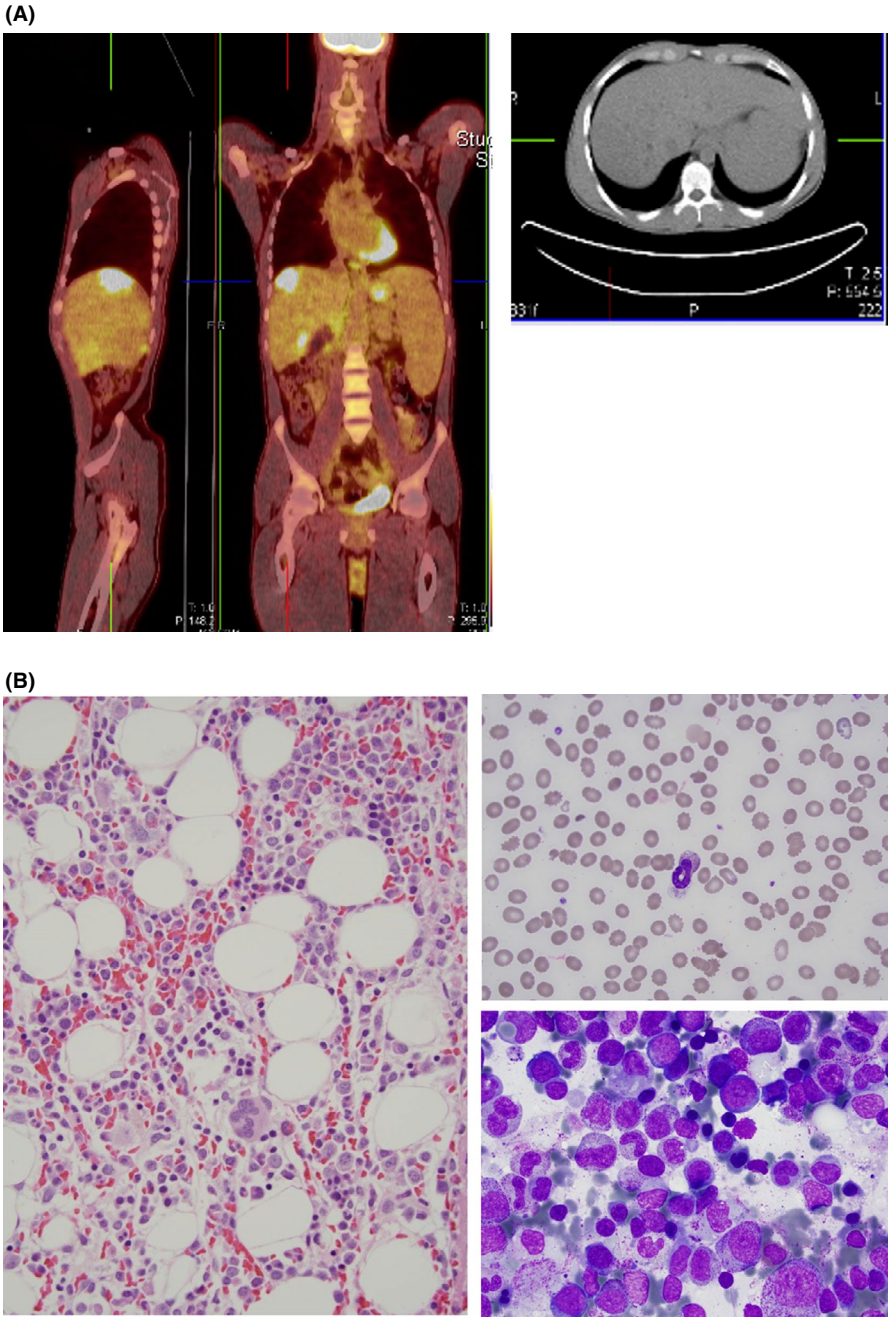

FIGURE 4 Hypersplenism in a 43-year-old man with cirrhosis, polycystic kidney disease, and mild neutropenia: (A) radiographic images demonstrating splenomegaly and (B) peripheral blood smear demonstrating neutropenia with normocellular BM aspirate and core biopsy demonstrating erythroid predominance

As such, an algorithm-based approach (Figures 5 and 6) may be helpful to achieve these ends. First, it is important to note that the causes of neutropenia vary depending on patient age. For this reason, the pediatric algorithm has important differences from the adult version.

6.1 | Clinical and laboratory workup of neutropenia in the pediatric population

In the neonatal period (from birth to 1 month of age), neutropenia is most frequently a consequence of genetics, intrauterine life, or the immediately postnatal microbiologic milieu (Figure 5).[46] It is particularly common in patients admitted to the neonatal intensive care unit (low ANC in ~8% of admissions) and in preterm infants (6%-58% affected).[47] Infection is by far the most common cause of neutropenia in this age group. In contrast to older children and immunocompetent adults, the neonatal response to infection is often a drop in the ANC. The reason for this is unknown, although it has been hypothesized that it is due to the small reserve of BM granulocytes. In contrast to neonatal sepsis, which is most often bacterial in origin, infection-related neonatal neutropenia is most often viral in origin.

The clinical workup of children begins with the determination of the magnitude of the ANC. For patients with an ANC < 0.55×10^9/L, antibiotic therapy and G-CSF may be indicated, since the diagnosis is most likely infection. In otherwise normal infants, another clinical consideration is chronic benign

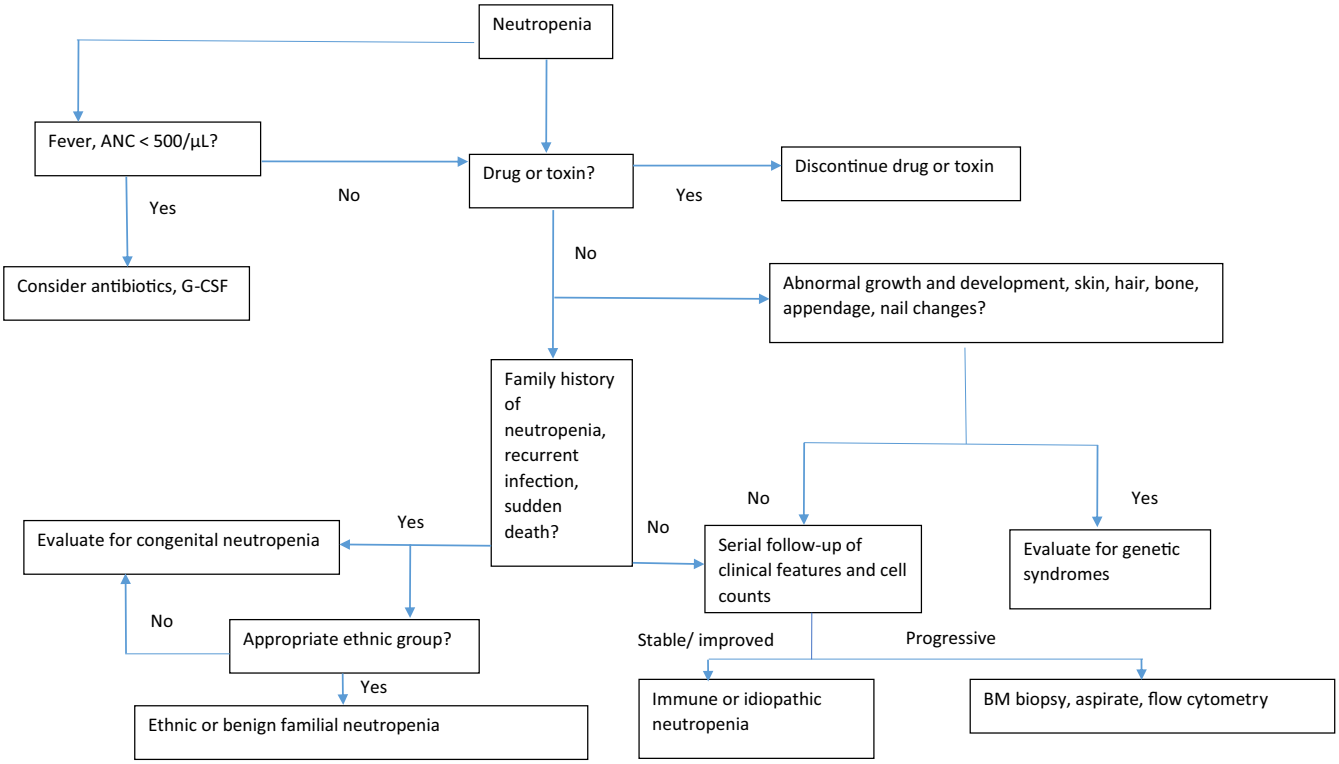

FIGURE 5 Diagnostic approach to neutropenia (pediatric) (adapted from Ref. [46]. For details, see text

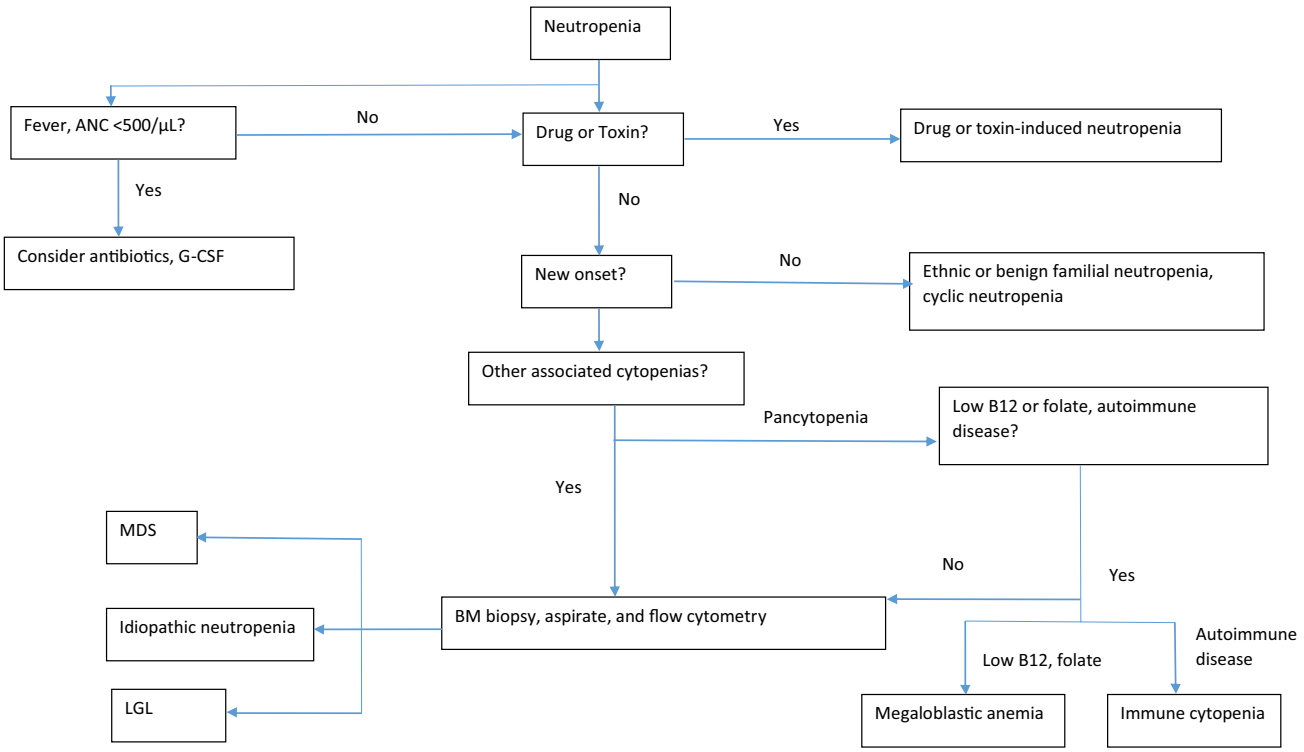

FIGURE 6 Diagnostic approach to neutropenia (adult) (adapted from Ref. [46]. For details, see text

neutropenia of infancy and childhood. Detection of antineutrophil antibodies would be useful in confirming the diagnosis; in these patients, prophylactic antibiotics may not be necessary due to low risk of infection. A third consideration is drug-induced neutropenia; clinical history of recent treatment with drugs known to cause neutropenia is important. In patients with physical findings

suggestive of genetic syndromes with associated neutropenia (eg, abnormal growth and development, skin, hair, bone, or nail abnormalities), genetic testing for Shwachman-Diamond syndrome, myelokathexis/neutropenia with tetraploid nuclei, reticular dysgenesis, dyskeratosis congenita, Chediak-Higashi syndrome, and other disorders may be indicated depending on findings. In individuals without these findings, serial assessment of the CBC can be performed. Improvement is suggestive of an immune-mediated neutropenia. If the patient is a member of an ethnic minority known to have a low ANC (eg, African American, Yemenite, Bedouin, Falasha Jewish), and other causes of neutropenia have been excluded, benign ethnic neutropenia may be the most likely diagnosis. In situations where the neutropenia is progressive or the etiology is unclear, BM biopsy with flow cytometric analysis and cytogenetics (including fluorescence in situ hybridization or other ancillary technologies) may be indicated to determine whether BM reserves are normal or decreased, and to exclude a malignancy.

6.2 | Clinical and laboratory workup of neutropenia in the adult population

The algorithm for adults takes into account that infection and drug-induced neutropenia are also common in this population (Figure 6).[46] Unlike younger patients, a higher percentage of clinically significant neutropenias are also due to malignancies and nutritional deficiencies. As with children, the first step is to determine the ANC. Patients with an ANC < 0.55×10^9/L are at significant risk of infection and may be candidates for intravenous antibiotics and G-CSF. A drug history is critical, with particular attention paid to the drugs commonly responsible for drug-induced neutropenia. Any prior CBC data should be reviewed. Otherwise normal patients with long-standing isolated neutropenia who are members of ethnic groups known to have low ANCs are likely to have benign ethnic neutropenia. Individuals with a periodic waxing and waning pattern of ANC may have cyclic neutropenia. In patients with additional cytopenias, especially mild thrombocytopenia and macrocytic anemia, the diagnosis of megaloblastic anemia should be considered. Serum B12, folate, copper, and zinc levels will be useful in establishing the diagnosis of megaloblastic anemia. Another possibility in these patients is autoimmune cytopenias, which can be related to a variety of disorders such as systemic lupus erythematosus. In patients with neutropenia with or without additional cytopenias unexplained by any of these disorders, BM biopsy with flow cytometric analysis and cytogenetics (including ancillary techniques such as fluorescence in situ hybridization) and next-generation sequencing may be indicated to diagnose malignancies such as myelodysplastic syndrome or T-LGL.

CONFLICT OF INTEREST

The author has no competing interest.

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