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Causes of neutrophilia

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INTRODUCTION — The normal total white blood cell (WBC) count in adults varies from 4400 to 11,000 cells/microL (4.4 to 11.0 x 10^9/L), the majority of which (approximately 60 percent) are mature neutrophils.

Leukocytosis is defined as a total WBC more than two standard deviations above the mean, or a value of greater than 11,000/microL in adults. Since the limits of normal include two standard deviations above the mean, 2.5 percent of the normal population will have a total WBC count above this value. This becomes important when an otherwise normal patient with a modest increase in WBC count is being evaluated. Such patients may be included with those considered to have chronic idiopathic neutrophilia (see below).

Neutrophilia, the major subject of this topic review, is defined as an increase in the absolute neutrophil count. It is most often seen in the setting of an increased total WBC count (see 'Definitions' below).

The major causes of neutrophilia will be reviewed here. The mechanisms of neutrophilia and the approach to the patient with this condition are discussed separately. (See "Definition and mechanisms of leukocytosis and neutrophilia" and "Approach to the patient with neutrophilia".)

DEFINITIONS — As stated above, leukocytosis is defined as a total white blood cell (WBC) count more than two standard deviations above the mean, or a value of greater than 11,000/microL in adults. While leukocytosis is most commonly due to an increase in the absolute number of mature neutrophils (neutrophilia), it can, on occasion, reflect a marked increase in the absolute numbers of lymphocytes, eosinophils, monocytes, or, more rarely, basophils.

By convention, leukocytosis to values in excess of 50,000 cells/microL, when due to causes other than leukemia, is termed a leukemoid reaction. Infection and the administration of hematopoietic growth factors or all-trans retinoic acid are the major causes of a leukemoid reaction.

Neutrophilic leukocytosis is defined as a total WBC greater than 11,000/microL plus an absolute neutrophil count (ANC) more than two standard deviations above the mean, or a value greater than 7700/microL in adults. (See "Definition and mechanisms of leukocytosis and neutrophilia".) The ANC is equal to the product of the WBC count and the percentage of polymorphonuclear cells (PMNs) and band forms noted on the differential analysis:

ANC (cells/microL) = WBC (cells/microL) x percent (PMNs + bands) ÷ 100

An ANC above 7700/microL in patient with a total WBC less than 11,000/microL is called isolated neutrophilia. An example of a setting in which this might occur is the patient with AIDS in whom an increase in neutrophils may be offset by the lymphopenia. However, for the purposes of this discussion, neutrophilia will be synonymous with neutrophilic leukocytosis.

Granulocytosis is generally used interchangeably with neutrophilia, although they are somewhat different. Granulocytosis can also reflect an increased WBC count due to increased numbers of eosinophils or basophils.

Causes of neutrophilia can be classified as primary (often due to an inherited defect) or secondary to another condition.

SPURIOUS LEUKOCYTOSIS — Before reviewing the causes of true neutrophilia, it is important to exclude artifacts that spuriously raise the observed white blood cell (WBC) count. This problem can be due to blood sampling problems or can occur in certain primary disease states.

Platelet clumping — If anticoagulation is inadequate, the resulting platelet clumps can be counted as leukocytes by automated cell counters. In these circumstances, the WBC count is rarely increased by more

than 10 percent and there is usually an associated spurious thrombocytopenia [1]. In addition, approximately 0.1 percent of normal subjects have EDTA-dependent agglutinins which can also lead to platelet clumping and spurious leukocytosis (also called pseudoleukocytosis) (picture 1) [2]. (See "Immune thrombocytopenia (ITP) in adults: Clinical manifestations and diagnosis", section on 'Diagnostic evaluation'.)

Cryoglobulinemia — When cold-insoluble plasma proteins are present, a temperature-dependent increase in leukocyte and platelet counts occurs at temperatures of 30°C or less. This can result in WBC counts as high as 50,000/microL and a doubling of the platelet count, both of which are attributed to various sizes of precipitated cryoglobulin particles [3]. This effect is increased if the sample is allowed to cool to lower temperatures and disappears if the sample is kept at body temperature.

PRIMARY NEUTROPHILIA — Neutrophilia, often with a left shift, can be indicative of a primary disease of the neutrophil system or abnormal regulation of neutrophil production (table 1).

Hereditary neutrophilia — An autosomal dominant condition leading to neutrophilia has been described in at least eight affected members of two families, with the following findings [4]:

- Leukocyte counts chronically in the 20,000 to more than 100,000/microL range
- Splenomegaly, often massive, occasionally requiring splenectomy
- Elevated leukocyte alkaline phosphatase (LAP) scores
- Widened diploe of the skull
- Normal neutrophil function and CD18/CD11b surface expression

No apparent propensity to bacterial infection has been reported and none of the family members has had any serious medical problems other than a bleeding diathesis related to platelet dysfunction [4].

Chronic idiopathic neutrophilia — Chronic neutrophilia can occur in individuals who are otherwise well. One report described 34 otherwise healthy individuals with total leukocyte counts of 11,000 to 40,000/microL, with the remainder of their blood counts being normal, other than occasional thrombocytosis [5]. Bone marrow aspirations and leukocyte alkaline phosphatase scores were normal. They were followed for more than 20 years with no apparent medical problems becoming evident.

These data are a reminder that certain normal individuals will fall outside the normal range with respect to white blood cell (WBC) count and should be considered normal, sparing them extensive evaluations.

Pelger-Huet anomaly — Pelger-Huet cells are morphologically abnormal neutrophils that have two lobes instead of the normal three to four lobes (picture 2). The two lobes are joined by a thin bridge that is much thinner than that seen in a normal band form. These cells function normally [6].

The Pelger-Huet anomaly is a benign dominantly inherited defect of terminal neutrophil differentiation with a frequency at birth of 1:6000, due to mutations in the lamin B-receptor gene [7,8]. An unusual case of Pelger-Huet anomaly has been reported in association with four generations of one family with late-onset progressive proximal muscular dystrophy [9].

The Pelger-Huet anomaly per se is not associated with neutrophilia, but it can give rise to an apparent increase in neutrophil band forms, which is often confused with a left shift (ie, as seen with infection). (See 'Acute infection' below.)

Most neutrophils in heterozygotes have nuclei with only two lobes and excessively coarse clumping of nuclear chromatin. The homozygous state results in neutrophils that contain a single round eccentric nucleus with clumped chromatin.

Colchicine and sulfonamides can induce the anomaly reversibly [10,11]. This so-called pseudo-Pelger cell has also been reported transiently during certain acute infections, in acute and chronic myeloid leukemia, and in myelofibrosis. This cell is especially prominent in the myelodysplastic syndromes, where this finding represents acquired defective maturation within the granulocyte series. Eosinophils, which are normally bilobed, and basophils may also be involved in this process.

Pelger-Huet cells can develop multiple lobes during states of vitamin B12 or folate deficiency [12]. The cells return to their bilobate state once the vitamin deficiency is corrected [12].

Familial myeloproliferative disease — A syndrome of growth retardation, hepatosplenomegaly, anemia and leukocytosis has been described [13]. All subjects had low LAP scores. Chromosomal analysis revealed no significant consistent abnormalities, and no subject had a Philadelphia chromosome. Some affected children died in early life, while others remained stable or improved. Several other members, in four generations of the family, had low LAP scores but no other findings.

Congenital anomalies and leukemoid reaction — Leukemoid reactions have been associated with amegakaryocytic thrombocytopenia and with congenital deformities such as tetralogy of Fallot, dextrocardia and absent radii, and rudimentary little toes [14,15].

Down syndrome — Infants with Down syndrome (trisomy of chromosome 21) may have transient leukemoid reactions that resemble congenital acute leukemia or chronic myeloid leukemia [16]. Affected children can also have exaggerated leukemoid responses to stress [17]. The mechanism by which this occurs is unclear.

Transient leukemoid reactions simulating acute leukemia have also been seen in three phenotypically normal children who expressed trisomy 21 mosaicism in myeloid cells but not in skin fibroblasts. The chromosomal abnormalities disappeared after the leukemoid reaction resolved [18,19].

Leukocyte adhesion deficiency — A small group of patients have been described with persistent leukocytosis, delayed separation of the umbilical cord, recurrent infections, and a stimulus-dependent activation defect of neutrophils. Leukocyte values of 5 to 20 times normal can be seen, often without an increase in bands.

Neutrophils from some patients with leukocyte adhesion deficiency (LAD) lack CD18 and therefore do not express any leukocyte or beta-2 integrins. This disorder is referred to as leukocyte adhesion deficiency type I (LAD I). A few other patients with similar and clinical laboratory findings have been described to have neutrophils lacking sialyl Lewis X, the ligand for L-selectin (LAD II). In LAD III, activation of all beta-integrins is defective. In spite of leukocytosis, neutrophils are not delivered to the site of infection because of adhesion and motility defects. These defects are discussed in detail separately. (See "Leukocyte-adhesion deficiency".)

One leukocyte integrin is the surface receptor for the inactivated third component of complement (C3bi); neutrophils from patients with LAD I show defects in chemotaxis, adherence, and phagocytosis of C3bi-coated particles [20]. (See "Primary disorders of phagocytic function: An overview".)

Familial cold autoinflammatory syndrome and Muckle-Wells syndrome — Familial cold autoinflammatory syndrome, also called familial cold urticaria, and the Muckle-Wells syndrome are two rare familial causes of neutrophilia. These disorders are discussed in detail separately, but will be briefly reviewed here. (See "Cryopyrin-associated periodic syndromes and related disorders".)

Familial cold autoinflammatory syndrome is characterized by episodes fever, leukocytosis, urticaria, rash, conjunctivitis, and muscle and skin tenderness after exposure to cold. Urticaria followed by fever starts about seven hours after cold exposure. Leukocytosis, sometimes to above 30,000/microL, starts about 10 hours after cold exposure and begins to subside 12 to 14 hours later [21,22]. The Muckle-Wells syndrome has a similar phenotype except for lack of cold sensitivity and frequent sensorineural hearing loss [23].

Both disorders are associated with mutations in a gene encoding for a protein called cryopyrin, which is a leukocyte-specific member of the pyrin superfamily that may play a role in the regulation of apoptosis in a subset of leukocytes involved in the early steps of inflammation [24-26].

Myeloproliferative neoplasms — Any of the myeloproliferative neoplasms (eg, chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, primary myelofibrosis) can be associated with neutrophilia. These disorders are discussed in detail separately. (See "Overview of the myeloproliferative neoplasms".)

Chronic myeloid leukemia — Chronic myeloid leukemia (CML) in adults may be distinguished from other causes of significant leukocytosis (WBC >50,000/microL) by presence of the following findings:

- Low LAP score (in contrast to the high values typically seen in infection and polycythemia vera)
- Presence of a greater percent of myelocytes than metamyelocytes on the WBC differential ("leukemic hiatus").
-

Presence of the Philadelphia chromosome (reciprocal translocation between chromosomes 9 and 22) on karyotypic analysis of the bone marrow, or molecular analysis for the bcr-abl fusion product of the CML translocation.

The diagnosis of CML is discussed in more detail separately. (See "Clinical manifestations and diagnosis of chronic myeloid leukemia".)

Other myeloproliferative disorders — Neutrophilia also may be seen in the other myeloproliferative disorders including polycythemia vera, primary myelofibrosis, and essential thrombocythemia.

In polycythemia vera, the increase in red cell mass and usual elevation in LAP score are distinguishing features from CML (table 2). (See "Clinical manifestations and diagnosis of polycythemia vera".)

In primary myelofibrosis, the primary features are marked splenomegaly and a leukoerythroblastic blood picture. (See "Clinical manifestations and diagnosis of primary myelofibrosis".)

In chronic neutrophilic leukemia, there is mature granulocytic proliferation in the blood and bone marrow, and an increased LAP score. (See "Clinical manifestations and diagnosis of chronic myeloid leukemia", section on 'Chronic neutrophilic leukemia'.)

SECONDARY NEUTROPHILIA — Neutrophilia can arise secondary to ongoing processes, such as smoking, infection, inflammation, medications, stress, and malignancy. This condition is called secondary or reactive neutrophilia (secondary or reactive leukocytosis).

Cigarette smoking — Perhaps the most common cause of mild neutrophilia is cigarette smoking. It has been estimated that the white blood cell (WBC) count in smokers is raised by about 25 percent, with an approximate doubling in the ANC in subjects who smoke two packs per day [27,28]. While the total WBC may stay elevated for up to five years after cessation of smoking [27,29], other observations have indicated normalization within one to two years [30,31]. The mechanism underlying this phenomenon is unknown, although smoking-related inflammation has been suggested [32].

Acute infection — Modest leukocytosis with a left shift (ie, presence of increased numbers of cells of the granulocyte series less mature than the neutrophil) is commonly seen in association with many acute bacterial infections. On the other hand, overwhelming infection can occasionally lead to depletion of the marrow's storage pool, resulting in neutropenia rather than neutrophilia. This is frequently noted in the preterm infant with overwhelming infection [33].

As an example, leukocytosis is commonly seen in association with acute otitis media. In one series in children, 9 percent had a WBC count >20,000/microL, while 27 percent had counts below the mean for age [34]. The predictive value of leukocytosis and increased band forms (WBC >15,000/microL and band forms >200/microL) in detecting bacterial infection was increased from 32 percent to 71 percent when decreased fibronectin levels (1 SD below mean for age) were also present. This finding is of particular interest in view of the role of fibronectin in promoting phagocytosis by neutrophils and monocytes [35].

Acute infection should be particularly suspected in patients with a total WBC count >25,000/microL. This was illustrated in a study of 54 such patients presenting to an emergency department who were compared with 118 age-matched controls who presented with moderate leukocytosis (WBC 12,000 to 25,000/microL) [36]. The patients with extreme leukocytosis were significantly more likely to have an infectious disease (74 versus 48 percent) and had a higher mortality rate.

Certain bacteria (eg, pneumococcus, staphylococcus, clostridial species) may cause particularly high leukocyte counts. Neutrophilia may be present in children with leptospiral infections, certain viral infections (Herpes simplex, varicella), advanced tuberculosis, and mononucleosis (particularly in the child younger than five years). Neutrophilia has also been observed in children with Kawasaki disease.

With respect to Clostridia infections, a leukemoid reaction is commonly seen in patients with Clostridium sordellii infection [37]. In addition, unexplained leukocytosis in hospitalized patients, even without diarrhea, may represent a harbinger of C. difficile infection, which usually occurs after 5 to 10 days of antibiotic treatment. (See "Clostridial myonecrosis", section on 'Spectrum of clostridial infections' and "Clostridium difficile infection in adults: Clinical manifestations and diagnosis", section on 'Clinical manifestations'.)

The acute elevation in the neutrophil count that may be seen with infection is due to the release of mature neutrophils and band forms from the marrow storage pool and the marginated pool, which can occur within minutes to hours. Epinephrine release may contribute to this response by diminishing neutrophil adherence to endothelium [38]. Granulocyte production also may be increased due in part to the following mechanisms:

- The pentapeptide pEEDCK (pGlu-Glu-Asp-Cys-Lys) is associated with mature leukocytes and maintains murine pluripotent hematopoietic stem cells (CFU-S) in a quiescent state under physiologic conditions. However, PMNs undergoing a respiratory burst oxidize pEEDCK to a disulfide-bonded homodimer, which stimulates CFU-S proliferation in vivo, providing a positive signal for increasing stem cell proliferation [39]. Thus, clinical settings such as infection that require increased hematopoiesis are associated sequentially with granulocyte and macrophage activation and the formation of dimer from endogenous pEEDCK monomer, providing a rapid signal for increasing stem cell proliferation and blood cell production.
- The leukemoid reaction seen with C. sordellii infection is mediated in part by C. sordellii neuraminidase, which directly stimulates promyelocyte cell proliferation [37]. The neuraminidase also affects vascular cell adhesion molecule 1, which promotes the release of mature and immature granulocytes from bone marrow stromal cells. (See "Toxic shock syndrome due to Clostridium sordellii".)

Reaction to infections or inflammation may also be accompanied by the presence of toxic granulation, Dohle bodies, and cytoplasmic vacuoles in the neutrophils (picture 3). The usefulness of these findings for diagnosing the presence of infectious or inflammatory disease was studied in 292 patients, using an elevated level of C-reactive protein as the gold standard for the presence of inflammatory disease [40]. The results indicated:

- The highest specificity for the presence of inflammatory disease (79 percent) was found when band forms comprised ≥20 percent of the total WBC
- The presence of Dohle bodies, toxic granulation, and cytoplasmic vacuoles had a high sensitivity (80 percent) but a low specificity (58 percent) for predicting inflammatory disease.

Chronic inflammation — Chronic inflammatory processes result in stimulation of granulocyte production. Examples include juvenile onset rheumatoid arthritis, Kawasaki's disease (in which a leukemoid reaction can occur), rheumatoid arthritis in adults, and adult Still's disease [41]. Patients with Crohn's disease, ulcerative colitis, granulomatous infections, bronchiectasis or chronic hepatitis may develop leukocytosis and/or neutrophilia, particularly with disease flare-ups. One study of 87 noncystic fibrosis bronchiectasis patients showed that the neutrophil count was the best correlate for active inflammation [42]. In another study of 110 patients at risk for recurrence of Crohn's disease following surgery, preoperative leukocytosis was significantly associated with recurrence [43].

Stress neutrophilia — A modest elevation in the neutrophil count has been associated with many types of "stress." Neutrophilia can occur within minutes of exercise, stress, or epinephrine injection and is presumed to be related to the movement of neutrophils from the marginated pool into the circulating pool [38,44,45]. With epinephrine, this effect is mediated by reduced neutrophil adherence and can be blocked in vivo with propranolol and in vitro with anti-cyclic AMP antibodies [38].

Exercise — A different mechanism appears to be involved with exercise-induced neutrophilia that is not blocked by propranolol, despite measurable increases in plasma epinephrine postexercise [46]. The neutrophilia in this setting is directly related to workload and cardiac output, suggesting a larger role for mechanical and flow-related effects on dislodgement of the leukocytes sequestered in the lung. On the other hand, the delayed leukocytosis (≤235 percent increase at five hours postexercise) may be related to marrow release of leukocytes [44,47]. The latter response is not associated with the release of early granulocyte precursors in the circulation [44].

Other — Neutrophilia has been associated with a variety of other stressful states:

- Newborns for the first three days post-delivery [48]
- Mild neutrophilia and lymphopenia have been associated with unipolar depression but may be related to the use of antidepressants [49].
- Neutrophilia is seen during the postoperative period, with the neutrophil count doubling approximately three hours after surgery. This response does not seem to be related to the type of anesthesia [50,51].

- Transient neutrophilia is often seen following seizures

Glucocorticoids and other drugs — Leukocytosis has been seen in association with a number of drugs and drug reactions:

- Glucocorticoid therapy is associated with a low-grade neutrophilia. The mean increase in ANC at prednisone doses of 40 to 80 mg/day is about 4000/microL [52]. This effect is mediated by reduced neutrophil adhesion and by increased release from marrow stores. (See "Definition and mechanisms of leukocytosis and neutrophilia", section on 'Neutrophil release and demargination'.)
- Beta-agonists such as epinephrine produce an acute neutrophilia by releasing neutrophils from the marginated pool [53]. This is similar to the stress-induced neutrophilic response described above.
- Lithium produces leukocytosis by increasing the production of colony stimulating factors; it has been used with varying success to treat several neutropenic states [54].
- Recombinant colony stimulating factors, such as rG-CSF and rGM-CSF are commercially available for increasing neutrophil counts in neutropenic patients undergoing chemotherapy. Absolute neutrophil counts above 10,000/microL can be regularly induced by their use.

Differentiation syndrome — Approximately 25 percent of patients with acute promyelocytic leukemia treated with tretinoin (all-trans retinoic acid, ATRA) have experienced a syndrome called the differentiation syndrome (previously retinoic acid syndrome). This consists of fever, dyspnea, weight gain, pulmonary infiltrates, pleural or pericardial effusions, episodic hypotension, renal dysfunction. The pathogenesis is unknown but may be related to a capillary leak syndrome induced by the release of cytokines from differentiating malignant promyelocytes. (See "Differentiation (retinoic acid) syndrome".)

During treatment with ATRA, up to 50 percent of patients will develop rapidly evolving leukocytosis, which is associated with a higher risk of life-threatening complications. The association between leukocytosis and the differentiation syndrome is unclear, although they often occur together [55]. The hyperleukocytosis probably results from cellular maturation and may result in leukostasis. Complications are uncertain and management is controversial. (See "Initial treatment of acute promyelocytic leukemia in adults", section on 'Differentiation syndrome' and "Initial treatment of acute promyelocytic leukemia in adults", section on 'Hyperleukocytosis' and "Hyperleukocytosis and leukostasis in hematologic malignancies".)

Marrow stimulation — Significant leukocytosis can be seen in states of chronic stimulation of the bone marrow, such as hemolytic anemia or immune thrombocytopenia [56]. As an example, patients with sickle cell anemia commonly have leukocyte counts in the 12,000 to 15,000/microL range and have an exaggerated elevation in WBC counts with infection or vasoocclusive crises [57]. This response may be further augmented by the functional asplenia (see below) commonly seen in sickle cell disease [58].

Significant rebound leukocytosis, lasting several weeks, can also occur during the recovery phase of marrow suppression [59,60]. In one extreme instance, 90 percent myeloblasts were transiently found in the bone marrow and as many as 20 percent myeloblasts in the peripheral blood [61].

Marrow invasion and leukoerythroblastic reaction — Neutrophilia associated with the presence of circulating immature granulocytes, nucleated red cells, and teardrop-shaped erythrocytes, with or without thrombocytosis (leukoerythroblastic reaction), may be seen when the marrow is directly invaded by tumor, fibrosis, or granulomatous reactions (picture 4A-B). A bone marrow aspiration and biopsy, performed to look for tumor clumps, fibrosis, granulomata, or culture for fungus or mycobacteria, is indicated in this setting [62]. A leukoerythroblastic reaction can also be transiently seen during recovery from severe myelosuppression and may be the initial presentation of transient erythroblastopenia of childhood [63].

Nonhematologic malignancy — Leukocytosis is frequently associated with solid tumors, particularly large cell lung cancer [64]. The elevation in WBC count seen with solid tumors is usually modest, in the 12,000 to 30,000/microL range [64-67]. However, counts as high as 115,000/microL occur; this can be seen in the absence of marrow metastasis or in patients with marrow involvement [68]. (See "Overview of the risk factors, pathology, and clinical manifestations of lung cancer", section on 'Paraneoplastic phenomena'.)

The etiology of extreme leukocytosis was explored in a retrospective study of 758 patients with solid tumors and a total WBC count >40,000/microL. The following causes were identified [69]:

- Use of hematopoietic growth factors — 69 percent
- Infection — 15 percent
- Paraneoplastic leukemoid reaction — 10 percent
- High-dose glucocorticoid and/or vasopressor use — 5 percent
- Newly-diagnosed leukemia — 1 percent

Paraneoplastic leukemoid reaction — In the above-noted study, nearly all of the 77 patients with paraneoplastic leukemoid reaction had either a large, bulky primary tumor or widely metastatic disease [69]. Their short-term prognosis was poor, with the vast majority dying within 12 weeks of their initial extreme leukocyte count.

The mechanisms of paraneoplastic leukemoid reaction are not well understood. In addition to bone marrow invasion and inflammation, some solid tumors have been shown to secrete substances with colony-stimulating activity (eg, G-CSF, GM-CSF, macrophage CSF) [70-72]. In murine models, both G-CSF and macrophage CSF have been isolated from tumors associated with marked neutrophilia [73].

Sweet syndrome — Sweet syndrome, also called acute febrile neutrophilic dermatosis, is characterized by fever, neutrophilia, and the abrupt appearance of erythematous, painful, cutaneous plaques, primarily on the upper extremities, head, and neck. It is associated with a variety of underlying conditions including malignancy in 20 to 25 percent of patients. (See "Sweet syndrome (acute febrile neutrophilic dermatosis): Pathogenesis, clinical manifestations, and diagnosis".)

Heatstroke — WBC counts as high as 30,000/microL have been seen in heatstroke. Up to 50 percent of the neutrophils have nuclei with segments smaller than usual, resembling a clustering of grapes around a central stem (ie, botryoid or grape-like nuclei) [74,75].

Asplenia — Moderate neutrophilia is often associated with asplenia, whether it is related to congenital disease (eg, dextrocardia), acquired disease (eg, autoinfarction in sickle cell disease [76]), or following surgical removal [77,78].

SUMMARY

- Neutrophilic leukocytosis is defined as a total white blood cell (WBC) count greater than 11,000/microL plus an absolute neutrophil count (ANC) greater than 7700/microL in adults. (See "Definition and mechanisms of leukocytosis and neutrophilia".) Neutrophilia can be either primary (inherited) or acquired (table 1).
- The most common causes of primary neutrophilia include the following (see 'Primary neutrophilia' above):
  - Hereditary neutrophilia (see 'Hereditary neutrophilia' above)
  - Familial myeloproliferative disease (see 'Familial myeloproliferative disease' above)
  - Congenital anomalies and leukemoid reactions (see 'Congenital anomalies and leukemoid reaction' above)
  - Down syndrome (see 'Down syndrome' above)
  - Leukocyte adhesion deficiency (see 'Leukocyte adhesion deficiency' above)
  - Familial cold autoinflammatory syndrome (see 'Familial cold autoinflammatory syndrome and Muckle-Wells syndrome' above)
- The most common causes of acquired neutrophilia include the following:
  - Cigarette smoking (see 'Cigarette smoking' above)
  - Acute or chronic infection or inflammation (see 'Acute infection' above and 'Congenital anomalies and leukemoid reaction' above)
  - Stress, exercise, or trauma (see 'Stress neutrophilia' above)

- Drugs (eg, glucocorticoids, epinephrine, granulocyte or granulocyte-macrophage colony-stimulating factor) (see 'Glucocorticoids and other drugs' above)
- Myeloproliferative neoplasms (eg, chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, primary myelofibrosis) or non-hematologic malignancy (see 'Myeloproliferative neoplasms' above and 'Nonhematologic malignancy' above and "Overview of the myeloproliferative neoplasms")
- Spurious (eg, platelet clumping, presence of cryoglobulins) (see 'Spurious leukocytosis' above)

- The mechanisms of neutrophilia and the evaluation of patients with neutrophilia and/or leukocytosis are discussed separately. (See "Definition and mechanisms of leukocytosis and neutrophilia" and "Approach to the patient with neutrophilia".)

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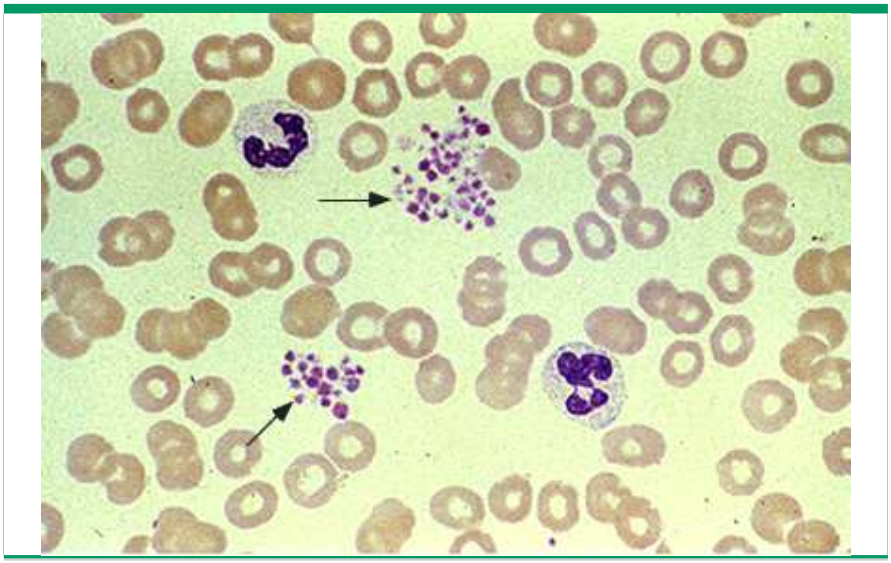
Topic 8377 Version 18.0

GRAPHICS

Pseudothrombocytopenia due to platelet clumping in EDTA

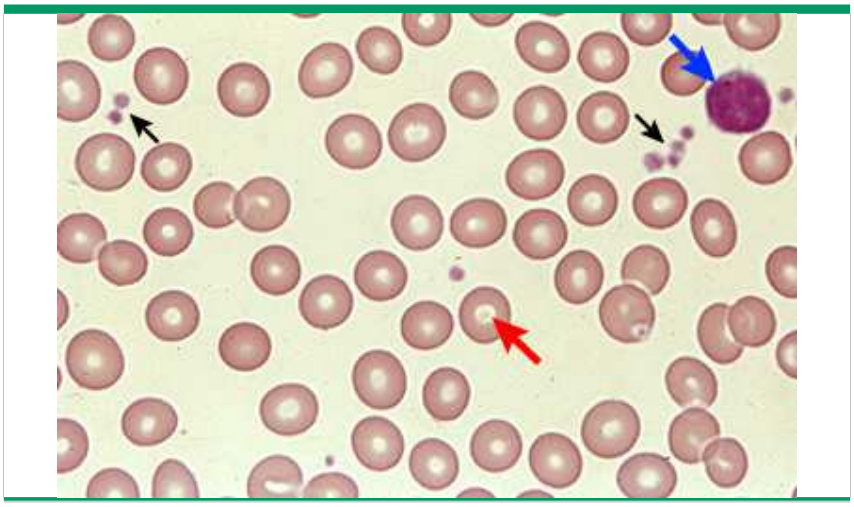


This peripheral blood smear shows platelet clumping (arrows) in an EDTA-anticoagulated blood sample. This patient had an EDTA-dependent platelet agglutinin which caused in vitro platelet clumping, resulting in an artifactually low platelet count (ie, "pseudothrombocytopenia"). No platelet clumping was seen, and the platelet count was normal, in a blood sample from this patient anticoagulated with sodium citrate.

Reproduced with permission from Beutler, E, Lichtman, MA, Coller, BS, et al, Hematology, 5th ed, McGraw-Hill, New York, 1995.

Graphic 68949 Version 2.0

Normal peripheral blood smear



High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the

nucleus of the small lymphocyte; central pallor (red arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 2.0

Classification of neutrophilia

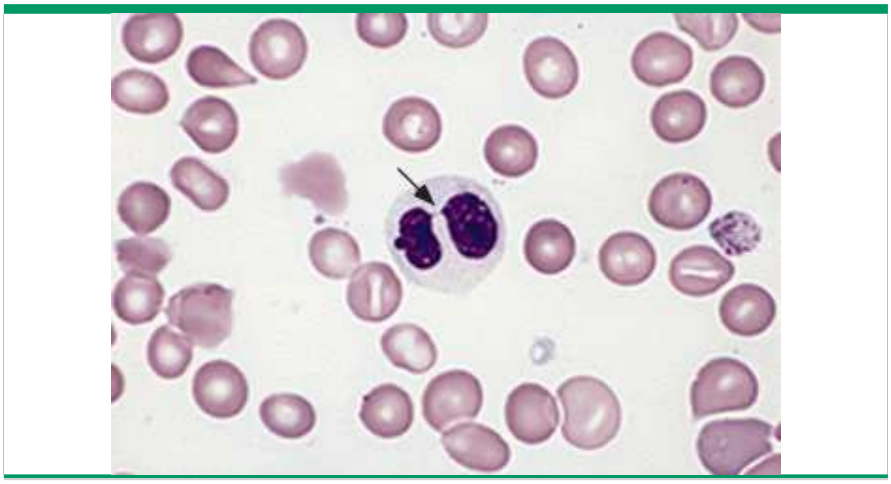
Spurious
Platelet clumping
Mixed cryoglobulinemia
Primary (no other evident associated disease)
Myeloproliferative disorders (eg, CML, PV, ET)
Hereditary neutrophilia
Chronic idiopathic neutrophilia
Familial myeloproliferative disease
Congenital anomalies and leukemoid reaction
Down syndrome
Leukocyte adhesion factor deficiency
Familial cold urticaria and leukocytosis
Secondary
Infection
Stress (physical or emotional stress, vigorous exercise)
Cigarette smoking
Drugs
Glucocorticoids
Recombinant G-CSF or GM-CSF*
Catecholamines (epinephrine)
Lithium
All-trans retinoic acid
Isolated case reports for occasional other drugs
Nonhematologic malignancy
Heatstroke
Generalized bone marrow stimulation (as in hemolysis)
Asplenia and hyposplenism

Most commonly encountered causes of neutrophilia are shown in **bold**.

CML: chronic myelogenous leukemia; PV: polycythemia vera; ET: essential thrombocythemia; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor.
* These agents are used therapeutically to raise the neutrophil count.

Graphic 80503 Version 3.0

Decreased nuclear lobes in myelodysplasia (pseudo Pelger-Huet anomaly)



Peripheral blood smear from a patient with refractory anemia with excess blasts (RAEB) shows a neutrophil with a bilobed pseudo-Pelger-Huet (Pelgeroid) nucleus. The two lobes are connected by a thin strand (arrow) giving a "pince-nez" appearance. These nuclei look identical to the those seen in the inherited Pelger-Huet anomaly. This neutrophil also has markedly reduced granulation, a finding commonly seen in the myelodysplastic syndromes.

From Brunning, RD, McKenna, RW. Tumors of the bone marrow. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 9, 1994, Washington, DC. Armed Forces Institute of Pathology.

Graphic 71990 Version 2.0

The Polycythemia Vera Study Group diagnostic criteria for polycythemia vera

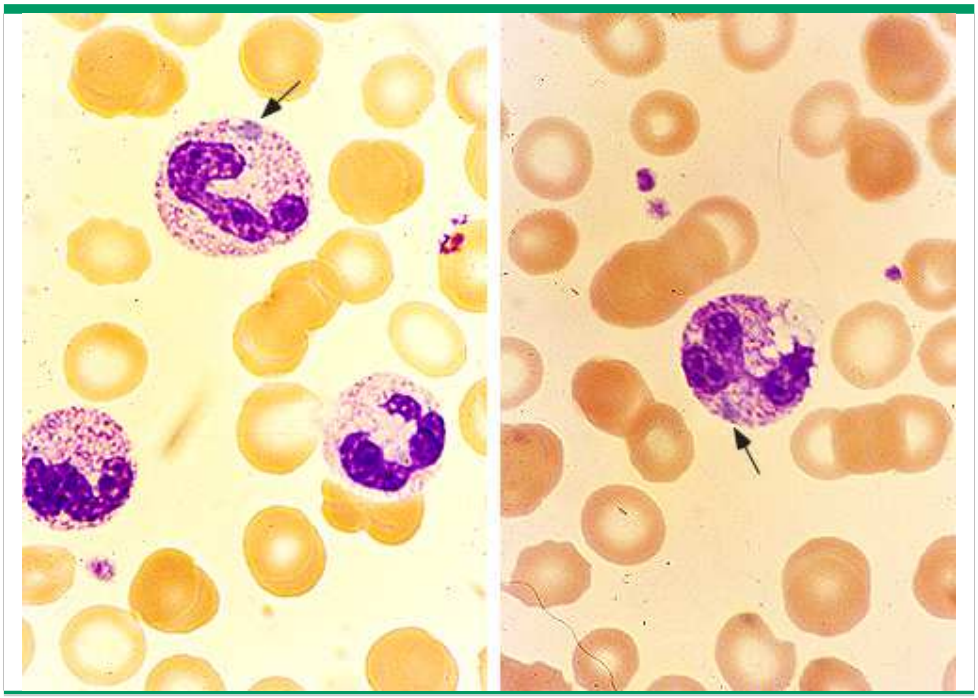
Major criteria
Increased red cell mass
Males: ≥36 mL/kg
Females: ≥32 mL/kg
Arterial oxygen saturation ≥92 percent
Splenomegaly
Minor criteria
Platelet count >400,000/microL
White blood cell count >12,000/microL*
Leukocyte alkaline phosphatase score >100*¶
Serum vitamin B12 >900 pg/mL **or** serum unbound B12 binding capacity >2200 pg/mL¶

The diagnosis of polycythemia vera requires the presence of all three major criteria or the presence of the first two major criteria and any two minor criteria.

* In the absence of fever or infection.
¶ Editor's note: These two minor criteria are not commonly used at the present time for making the diagnosis of polycythemia vera.

Graphic 62788 Version 2.0

Toxic granulations and Döhle bodies in infection/inflammation

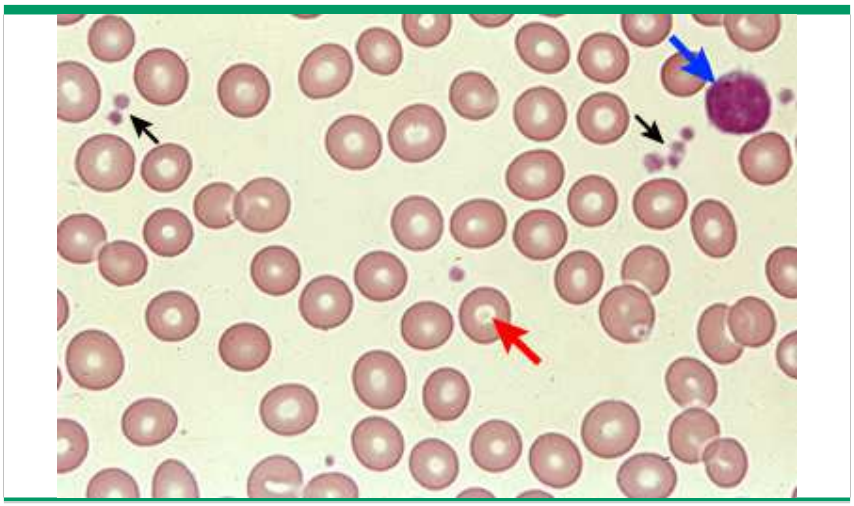


Left panel: Peripheral blood smear shows neutrophils with toxic granulations, which are dark coarse granules. A Döhle body is also seen (arrow). Right panel: A neutrophil with toxic granulations, vacuoles (another toxic change), and a Döhle body (arrow). These abnormalities are characteristic of toxic systemic illnesses.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 70248 Version 2.0

Normal peripheral blood smear

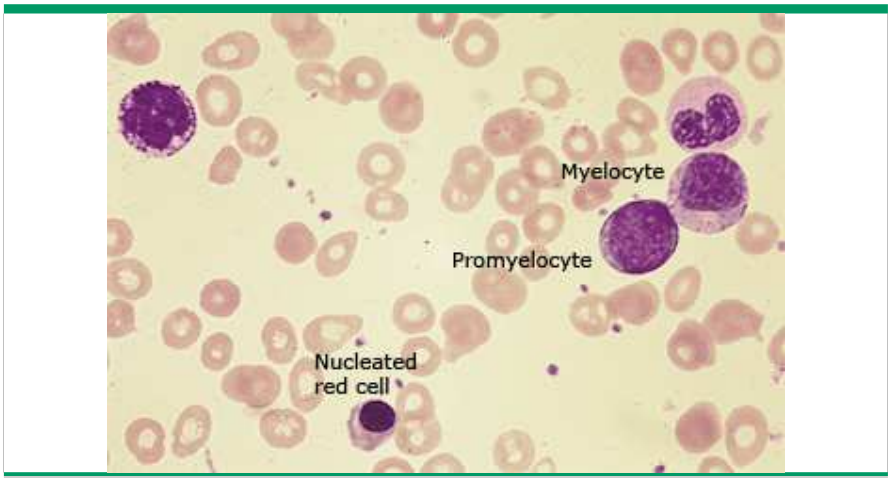


High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (red arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 2.0

Leukoerythroblastic peripheral blood smear

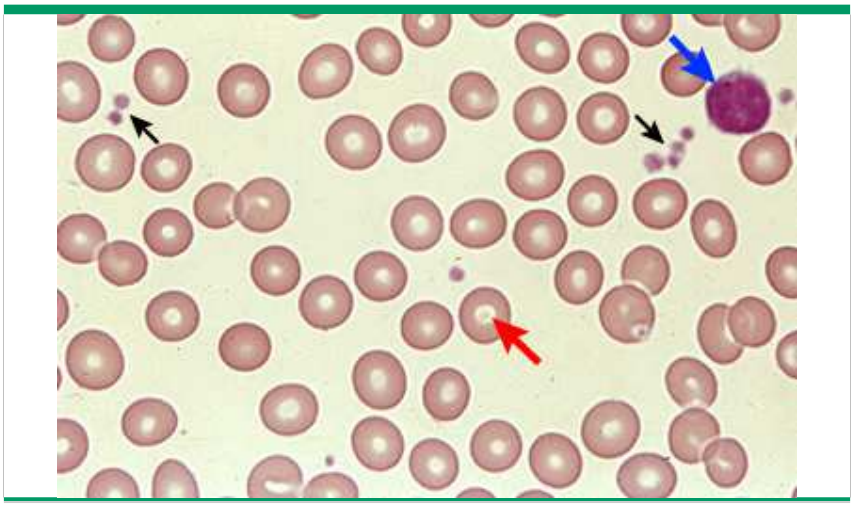


Leukoerythroblastic peripheral blood smear showing the presence of nucleated red cells and immature white cells. This pattern occurs with marrow replacement, usually due to fibrosis that may be idiopathic (eg, primary myelofibrosis) or reactive to conditions such as metastatic cancer.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 68110 Version 3.0

Normal peripheral blood smear

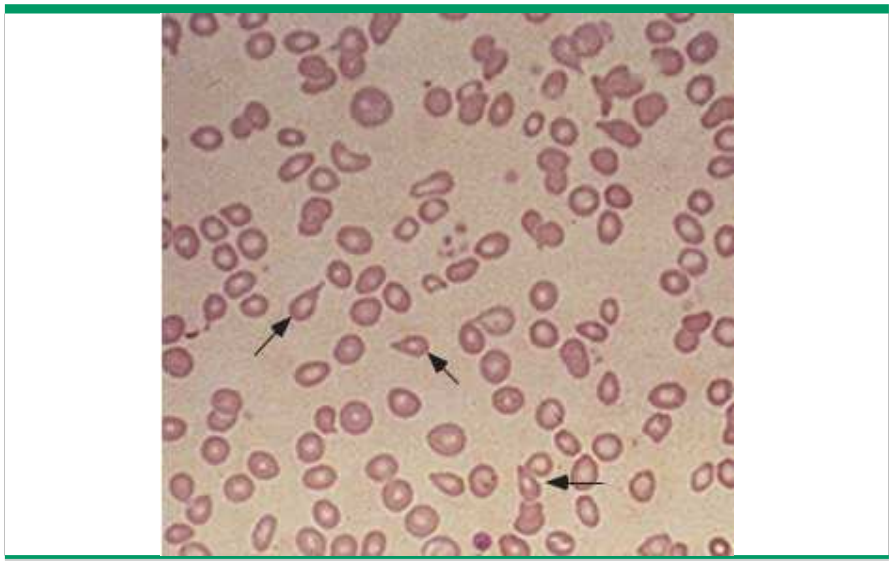


High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (red arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 2.0

Teardrop-shaped red blood cells (dacrocytes)

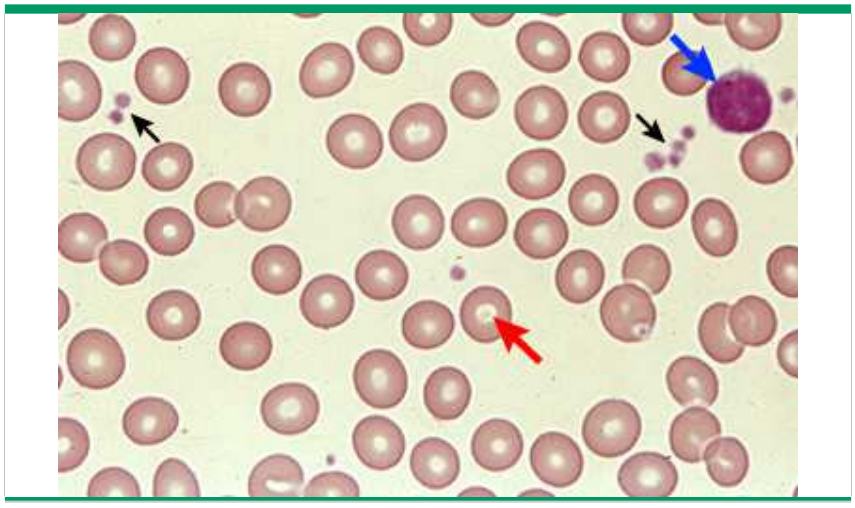


This peripheral smear from a patient with bone marrow fibrosis shows numerous teardrop-shaped red cells (arrows). Note that the teardrops are pointed in several different directions, ruling out an artifact due to preparation of the smear.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 55274 Version 4.0

Normal peripheral blood smear



High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (red arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

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Disclosures

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CSF)]. Equity Ownership/Stock Options (spouse): Amgen [chronic neutropenia (Filgrastim)]. Other Financial Interest: Hem/Onc Today (pediatric hematology journal). **Jennifer S Tirnauer, MD** Nothing to disclose.

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