Approach to the patient with 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. By convention, leukocytosis to values in excess of 50,000 cells/microL, when due to causes other than leukemia, is termed a leukemoid reaction or hyperleukocytosis.

While leukocytosis is most commonly due to an increase in the absolute number of mature neutrophils (neutrophilia), it can also reflect a marked increase in the absolute numbers of lymphocytes, eosinophils, monocytes, or, more rarely, basophils. Granulocytosis is generally used interchangeably with neutrophilia, although the two terms are somewhat different, since granulocytosis can also reflect leukocytosis due to increased numbers of eosinophils or basophils.

The absolute neutrophil count (ANC) is equal to the product of the white blood cell count (WBC) and the percentage of polymorphonuclear cells (PMNs) and band forms noted on the WBC differential, and is calculated as follows:

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

Neutrophilic leukocytosis is defined as a total WBC greater than 11,000/microL plus an 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".)

An ANC above 7700/microL in patient with a total WBC less than 11,000/microL is called 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 presence of significant lymphopenia. However, for the purposes of this discussion, neutrophilia will be synonymous with neutrophilic leukocytosis.

This topic review will present a clinical approach to the patient with neutrophilia. The causes of this disorder are discussed separately (table 1). (See "Causes of neutrophilia".)

INITIAL APPROACH — As is true for the approach to any medical problem, there is no substitute for an accurate history and physical examination. However, before this process is started, the clinician must make sure that there is no laboratory error involved. Specifically, blood counts that do not make sense within the context of the clinical findings should be repeated before extensive evaluation is undertaken.

The history — Certain conditions associated with neutrophilia are obvious and should be immediately recognized by the clinician (table 1). (See "Causes of neutrophilia".)

- Any active inflammatory condition or infection
- Cigarette smoking, which may be the most common cause of mild neutrophilia
- Pregnancy and following uncomplicated spontaneous or cesarean delivery
- Previously diagnosed hematologic disease (such as acute and chronic leukemias, chronic myeloproliferative or myelodysplastic disease)
- The presence of, and treatment for, a chronic anxiety state, panic disorder, rage, or emotional stress (eg, posttraumatic stress disorder, depression)
- Recent vigorous exercise
- Recent thermal burn, electric shock, surgery, or trauma
- Presence of non-hematologic diseases known to increase neutrophil counts (eg, eclampsia, thyroid storm, hypercortisolism).

- Prior splenectomy or known asplenia
- Positive family history of neutrophilia
- Post-antibiotic diarrhea (see 'Medications' below)
- Recent vaccination or snake bite
- Sickle cell disease, in which leukocytosis within the first two years of life, in the absence of infection, predicts for increased disease severity [1]

Medications — Various medications may cause neutrophilia. However, with the exception of the drugs listed in the table (table 1), such cases are rare and appear in the literature as isolated case reports. Nevertheless, it is good practice to search for such adverse effects through the pharmacy literature, especially when the patient is taking a medication whose side effects may not be widely known, or when the timing of onset of neutrophilia coincides with the institution of the medication.

Unexplained leukocytosis in hospitalized patients, even without diarrhea, may represent a harbinger of C. difficile infection, which usually occur after 5 to 10 days of antibiotic treatment. Thus, testing for C. difficile infection may be reasonable in such patients. (See "Clostridium difficile infection in adults: Clinical manifestations and diagnosis", section on 'Clinical manifestations' and "Clostridium difficile infection in adults: Clinical manifestations and diagnosis", section on 'Differential diagnosis'.)

The physical examination — The most important function of the physical examination, as regards the presence of neutrophilia, is to determine the presence or absence of infection, inflammation, or malignancy. Clues to the presence of such disorders include, but are not limited to, the following:

- Fever
- Hypotension, shock, tachycardia, hypothermia (eg, overwhelming sepsis)
- Abscess or evidence of infection at any site
- Abdominal rebound tenderness
- Signs of pulmonary consolidation or pleural effusion
- Joint swelling, erythema, tenderness
- Hepatosplenomegaly
- Lymphadenopathy
- Diarrhea (eg, C. difficile infection)

Findings such as the above indicate the presence of significant disease, and require appropriate diagnostic workup, consultation, and/or hospitalization of the patient.

INITIAL LABORATORY TESTING — This discussion presupposes that the patient is known to have an increased ANC as usually determined by an automated cell counter. The evaluation of this abnormal laboratory finding should begin with consideration of normal variation and spurious leukocytosis. Measurement of the sedimentation rate (ESR) and C-reactive protein (CRP), both of which are elevated in inflammation and infection, can be very helpful, particularly in an asymptomatic patient with leukocytosis.

Normal variation — A number of factors contribute to the wide variability in neutrophil counts in normal populations. Particularly in the asymptomatic patient with persistent mild neutrophilia, one must remember that, by definition, the WBC count in 2.5 percent of the normal population will be greater than two standard deviations above the mean (ie, >11,000/microL). Since regulation of granulocyte production is in part genetically controlled, examination of the parents' or siblings' blood counts may be of help in these situations [2,3].

As an example, one report described 34 otherwise healthy subjects with total leukocyte counts of 11,000 to 40,000/microL, with the remainder of their blood counts being normal, other than occasional thrombocytosis [2]. Bone marrow aspirations and leukocyte alkaline phosphatase scores were normal. The subjects were followed for more than 20 years with no apparent medical problems becoming evident.

Spurious leukocytosis — Artifacts which spuriously raise the observed WBC can be seen due to blood sampling problems or in certain primary disease states.

Platelet clumping — Clumping of platelets, leading to artifactually high white blood cell counts, can occur under the following circumstances:

- If anticoagulation of the sample is inadequate, the resulting platelet clumps can be counted as leukocytes by some automated cell counters. As a result, the WBC count is rarely increased by more than 10 percent and there is usually an associated spurious thrombocytopenia [4].
- Approximately 0.1 percent of normal subjects have EDTA-dependent agglutinins which can lead to platelet clumping and spurious leukocytosis (also called pseudoleukocytosis) (picture 1) [5]. (See "Immune thrombocytopenia (ITP) in adults: Clinical manifestations and diagnosis", section on 'Diagnostic evaluation'.)

An examination of the peripheral smear which shows platelet clumping is consistent with the presence of one of these artifacts. A repeat blood sample adequately anticoagulated with citrate or heparin (rather than EDTA) should help resolve this problem.

Cryoglobulinemia — When cold-insoluble plasma proteins are present, a temperature-dependent increase in leukocyte and platelet counts occurs at temperatures of 30ºC 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 [6]. This effect is increased if the sample is allowed to cool to lower temperatures and disappears if the sample is kept at body temperature.

EVALUATION OF THE COMPLETE BLOOD COUNT — The finding of neutrophilia requires that the patient has had (at least) a total WBC count and a WBC differential performed, either manually or via an automated cell counter. Thus, the clinician almost always has additional information at hand with which to evaluate the finding of neutrophilia. This will depend upon the methodology used, although most blood counts are now performed using automated cell counters, all of which employ computer programs for "flagging" abnormalities (eg, multipart differential counts, presence of immature cells and blasts, left shift indicators, cells with increased peroxidase activity, lobularity index, and the presence of nucleated red blood cells) [7]. (See "Automated hematology instrumentation".)

In many cases, automated differential WBC counts will be superior to 100 cell manual differential counts, since the former can sample and evaluate up to 10,000 nucleated cells, with resulting increases in precision. As an example, in a patient with a WBC of 10,000/microL and 60 percent neutrophils, the coefficient of variation for the ANC will be 13 and 1.3 percent for a 100 and 10,000 cell differential, respectively. However, small numbers of immature cells of the neutrophil series and the presence of a "left shift" (usually defined as a band form count greater than 700/microL) may be missed with all methods. A well prepared blood smear examined by a trained clinician or laboratorian can add significant information under such circumstances. (See "Evaluation of the peripheral blood smear".)

Detection of infection or inflammation — The usefulness of other parameters on the blood count for diagnosing the presence of infectious or inflammatory disease (ID) was studied in 292 patients, using an elevated level of C-reactive protein (CRP) as the gold standard for the presence of ID [8]. Study parameters included a manual 200 cell differential count of neutrophil band forms, machine-derived WBC and neutrophil counts, and the "left shift" parameters from two different automated counters. The results indicated:

- The highest specificity for the presence of ID (79 percent) was found for a manual band count ≥20 percent of the total WBC and the left shift flag from the Technicon H-1 analyzer.
- The highest sensitivity for the presence of ID (80 percent) was the presence of Dohle bodies, toxic granulation, and cytoplasmic vacuoles from manual examination of the peripheral smear (picture 2 and picture 3) and the left-shift indicator of the Coulter MAX M analyzer.

A second study, employing results from preoperative blood counts in 40 patients with a clinical diagnosis of acute appendicitis, 33 of whom showed acute inflammation histologically, also indicated a sensitivity of 79 percent for the Technicon H-1 analyzer's left shift flag [9]. However, the highest sensitivity (91 percent) for predicting the presence of acute inflammation was a total WBC count above 10,500/microL.

Similar findings were noted in a blinded preoperative study of 204 patients with suspected acute appendicitis [10]. The highest sensitivity (83 percent) for predicting the presence of acute appendicitis was the total WBC count. The sensitivity of testing could be increased to 100 percent by employing an elevated WBC or an elevated CRP or an increased neutrophil percentage as a single parameter. However, this lowered specificity and decreased the positive predictive value to 37 percent. The same triple test combination had a negative

predictive value of 100 percent, indicating that appendicitis is unlikely when all three tests are simultaneously negative (normal).

Based on personal experience, the leukocyte counts can be as high as 80,000 to 100,000/microL in patients with infection or inflammation. The leukocytosis usually decreases within a couple of days of starting treatment. As long as the counts are decreasing in response to therapy, the leukocytosis is likely to be reactive. Evaluation of the ESR and CRP are particularly helpful in detecting occult inflammation.

Complete blood counts in family members — Familial neutrophilia has been reported, as has chronic idiopathic neutrophilia. (See "Causes of neutrophilia", section on 'Primary neutrophilia'.)

Combined abnormalities on the complete blood count — The following additional findings on the differential count and the CBC can be of importance in evaluation of the neutrophilic patient:

Anemia — The combination of anemia and neutrophilia is a nonspecific finding, and can be seen in many different settings, such as chronic infection or inflammation, hemolytic anemia, and malignancies. Clues to the diagnosis may be available on examination of the peripheral smear or evaluation of the red blood cell (RBC) indices. (See "Evaluation of the peripheral blood smear" and "Approach to the adult patient with anemia" and "Approach to the child with anemia".)

Increased hematocrit — The combination of neutrophilia and polycythemia suggests the presence of polycythemia vera. Associated findings on the complete blood count, such as microcytic RBC indices, thrombocytosis, basophilia, and/or eosinophilia, and small numbers of immature cells of the granulocyte series are often seen (table 1). (See "Clinical manifestations and diagnosis of polycythemia vera".)

Increased platelet count — The combination of neutrophilia and an elevated platelet count does not necessarily add significant information, since both elements can be increased in infectious, inflammatory, or malignant conditions, or following periods of marrow recovery (see below). However, this combination in an asymptomatic patient may suggest the presence of essential thrombocythemia (primary thrombocytosis). (See "Approach to the patient with thrombocytosis" and "Diagnosis and clinical manifestations of essential thrombocythemia".)

Decreased platelet count — The combination of neutrophilia and thrombocytopenia is most frequently seen in sepsis due to acute bacterial infection, with or without disseminated intravascular coagulation. Associated findings on the peripheral smear are a pronounced left shift plus changes in the neutrophils, such as toxic granulations, Dohle bodies, and cytoplasmic vacuoles (picture 2).

An important and potentially fatal but treatable condition which can present with this combination is a thrombotic microangiopathy such as hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP). Associated findings on the CBC and peripheral smear are the presence of microangiopathic RBC changes (ie, hemolytic anemia, fragmented RBCs, reticulocytosis), and the presence of enlarged platelets (picture 4). The WBC is elevated in about 50 percent of patients with HUS, occasionally to levels above 20,000/microL; neutrophilia may be associated with a poor outcome in children [11,12]. (See "Overview of hemolytic uremic syndrome in children".)

The combined presence of thrombocytopenia and microangiopathic hemolytic anemia (MAHA) without another clinically apparent etiology is sufficient to suspect the diagnosis of TTP and initiate urgent hematologic consultation and plasma exchange. (See "Approach to the patient with suspected TTP, HUS, or other thrombotic microangiopathy (TMA)", section on 'Immediate management decisions'.)

Nucleated RBC and leukoerythroblastic picture — The combination of neutrophilia and nucleated red blood cells in a patient without a primary hematologic disorder can be an ominous sign. It is seen most often in septic shock.

Neutrophilia and nucleated red blood cells may also be associated with teardrop shaped RBCs and early granulocytes in the blood, the so-called leukoerythroblastic blood picture (picture 5A-B). This combination suggests the presence of infiltrative marrow disease (eg, myelofibrosis, malignancy, granulomatous disease).

Left shift in the WBC differential — The standard definition of a left shift is a band form count greater than 700/microL, a condition often called "bandemia." As an example, a band to total neutrophil count ratio greater than 0.16 is significantly associated with neonatal sepsis [13]. In infection, cells as immature as

metamyelocytes are often seen on the peripheral smear, but it is unusual to see more immature cells (eg, myelocytes, promyelocytes, and blasts) in such a setting. When these latter cells are present, they indicate a "severe left shift", most likely due to the presence of an acute or chronic myeloproliferative disorder, such as chronic myeloid leukemia, idiopathic myelofibrosis, or one of the various forms of acute leukemia.

Monocytosis — Monocytes normally comprise less than 10 percent of total circulating white cells, with the absolute monocyte count being <800/microL in the normal adult.

A number of conditions which cause neutrophilia can also cause monocytosis, making this combination a relatively nonspecific finding. These include pregnancy, the asplenic state, inflammatory (eg, sarcoidosis, inflammatory bowel disease) and autoimmune conditions, depression, and treatment with corticosteroids or colony stimulating factors. Monocytosis may also accompany conditions associated with neutropenia, presumably as a compensatory mechanism [14].

A large number of infections have been associated with monocytosis including brucellosis, varicella-zoster, bacterial endocarditis, tuberculosis, malaria, typhoid fever, syphilis, and trypanosomiasis.

Monocytosis may also be seen in certain malignancies, such as Hodgkin lymphoma. Neutrophilia with monocytosis may also suggest chronic myelomonocytic leukemia, one of the myelodysplastic disorders. Additional associated findings in this condition are anemia, thrombocytopenia and abnormal cellular maturation (eg, macrocytic red cells, defective lobulation in neutrophils, and abnormal size and granulation in platelets). (See "Clinical manifestations and diagnosis of the myelodysplastic syndromes", section on 'Bone marrow aspirate' and "Chronic myelomonocytic leukemia".)

Monocytosis also may be seen in some forms of chronic myeloid leukemia as well as in the myelomonocytic and monoblastic variants of acute myeloid leukemia. (See "Clinical manifestations and diagnosis of chronic myeloid leukemia" and "Clinical manifestations, pathologic features, and diagnosis of acute myeloid leukemia", section on 'Diagnosis'.)

Bone marrow examination — Examination of the bone marrow is of little help in evaluating the patient with neutrophilia, except in certain instances of leukemoid reactions, leukoerythroblastic blood picture, or the presence of immature cells (ie, blasts and other cells more immature than the metamyelocyte) on the peripheral smear (picture 5A-B). (See 'Nucleated RBC and leukoerythroblastic picture' above.)

Bone marrow biopsy should be included in these situations, as well as fungal and mycobacterial cultures. The biopsy may reveal granuloma, which may intensify the search for fungal infection or metastatic tumor that might be missed in a marrow aspirate.

Other tests — Other ancillary tests may on occasion be of value in assessing the presence or absence of infection or inflammation, although a "gold standard" is not generally agreed upon. The most commonly employed tests for this purpose include serum C-reactive protein and the erythrocyte sedimentation rate. Other tests, which may not be generally available include plasma fibronectin concentration, neutrophil CD16 expression, and the percentage of cells of the neutrophil series with a high content of peroxidase. (See "Acute phase reactants".)

The leukocyte alkaline phosphatase (LAP) score, which is high in infection, inflammation, and polycythemia vera (PV) and low in chronic myeloid leukemia (CML) and paroxysmal nocturnal hemoglobinuria, may also be of help. It must be kept in mind, however, that the LAP score can be normal in PV and CML, particularly juvenile CML. Normal ranges for the LAP vary among laboratories; results may be unreliable in laboratories with minimal experience in performing the test. (See "Clinical manifestations and diagnosis of polycythemia vera".)

Existing radiotracer techniques to study neutrophil kinetics, although sophisticated, are not of much clinical use. Similarly, clinical tests such as hydrocortisone (or prednisone) challenge or epinephrine stimulation, which reflect the presence of a releasable marrow storage pool or marginated pool, respectively, have limited differential diagnostic power and are not performed clinically.

HYPERLEUKOCYTOSIS — The question arises concerning the level at which an extremely high WBC count (hyperleukocytosis, leukemoid reaction) can cause symptoms and warrant the consideration of **emergency** leukapheresis. Patients with neutrophil counts above 250,000/microL may require urgent hematologic

consultation and intervention to prevent the vasoocclusive complications of hyperviscosity. In contrast, leukemic blast cells, because of their nondeformability, cause hyperviscosity at lower cell counts (approximately 75,000/microL). This is an unusual presenting problem because patients with rapidly evolving leukemia typically present with problems such as hemorrhage or thrombosis at considerably lower blast counts. (See "Hyperleukocytosis and leukostasis in hematologic malignancies".)

SUMMARY

- The normal total white blood cell (WBC) count in adults varies from 4400 to 11,000 cells/microL. Leukocytosis is defined as a total WBC greater than 11,000/microL in adults. We use neutrophilia to refer to an absolute neutrophil count >7700/microL. (See 'Introduction' above.)
- Leukocytosis to values in excess of 50,000 cells/microL, when due to causes other than leukemia, is termed a leukemoid reaction or hyperleukocytosis. (See 'Hyperleukocytosis' above.)
- The following are major causes of neutrophilia (table 1). Many will be obvious by history or physical examination. (See 'Initial approach' above.)
    - Any active inflammatory condition or infection
    - Cigarette smoking, which may be the most common cause of mild neutrophilia
    - Pregnancy and following uncomplicated spontaneous or cesarean delivery
    - Previously diagnosed hematologic disease
    - Certain medications (eg, glucocorticoids, catecholamines)
    - The presence of, and treatment for, a chronic anxiety state, panic disorder, rage, or emotional stress
    - Recent vigorous exercise, thermal burn, electric shock, surgery, or trauma
    - Laboratory artifact (eg, platelet clumping, cryoglobulinemia)
- Evaluation of a patient with leukocytosis should include a complete blood count, platelet count, WBC differential and examination of the peripheral blood smear as a minimum. Items to evaluate include:
    - Presence of a “left shift” in the WBC differential (see 'Left shift in the WBC differential' above)
    - Evaluation for infection/inflammation (see 'Detection of infection or inflammation' above and 'Other tests' above)
    - Presence of anemia or polycythemia, thrombocytopenia or thrombocytosis, and/ or abnormal cells (eg, nucleated red cells, blasts, increased monocytes, atypical lymphocytes) (see 'Combined abnormalities on the complete blood count' above)
    - Presence of predominance of lymphocytes, especially in a child over five years of age (young children normally have a predominance of lymphocytes) (see "Approach to the child with lymphocytosis or lymphocytopenia")
- Elevation of the erythrocyte sedimentation rate or C-reactive protein may indicate occult inflammatory disease. (See 'Detection of infection or inflammation' above.)
- Examination of the bone marrow is of little help in evaluating the patient with neutrophilia, except in certain instances of leukemoid reactions, leukoerythroblastic blood picture, or the presence of immature cells (ie, blasts and other cells more immature than the metamyelocyte) on the peripheral smear (picture 5A-B). (See 'Bone marrow examination' above.)

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Topic 8381 Version 17.0

GRAPHICS

Classification of neutrophilia

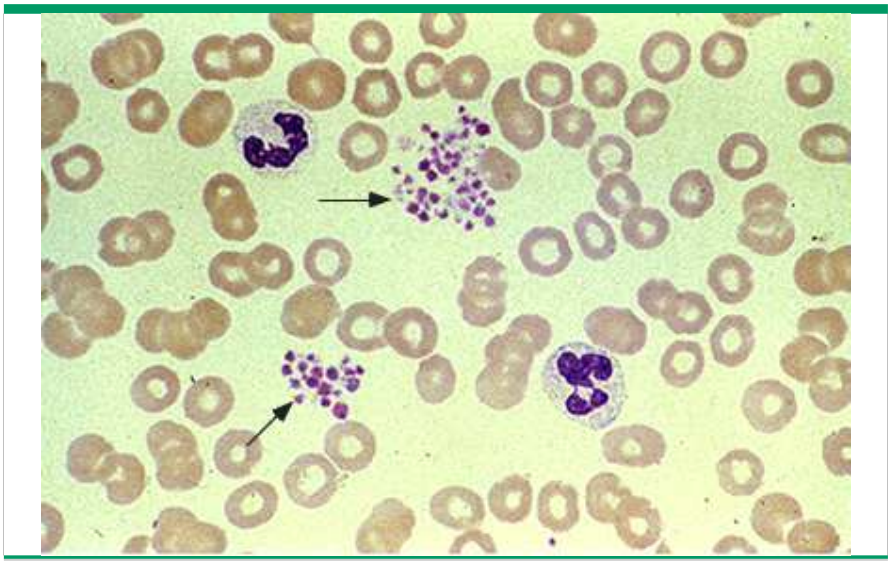
Spurious
Platelet clumping
Mixed cryoglobulinemia
Primary (no other evident associated disease)
Myeloproliferative disorders (eg, CML, PV, ET)
Hereditary neutrophilia
Chronic idiopathic neutrophilia
Familial myeloproliferative disease
Congenital anomalies and leukemoid reaction
Down syndrome
Leukocyte 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

Pseudothrombocytopenia due to platelet clumping in EDTA

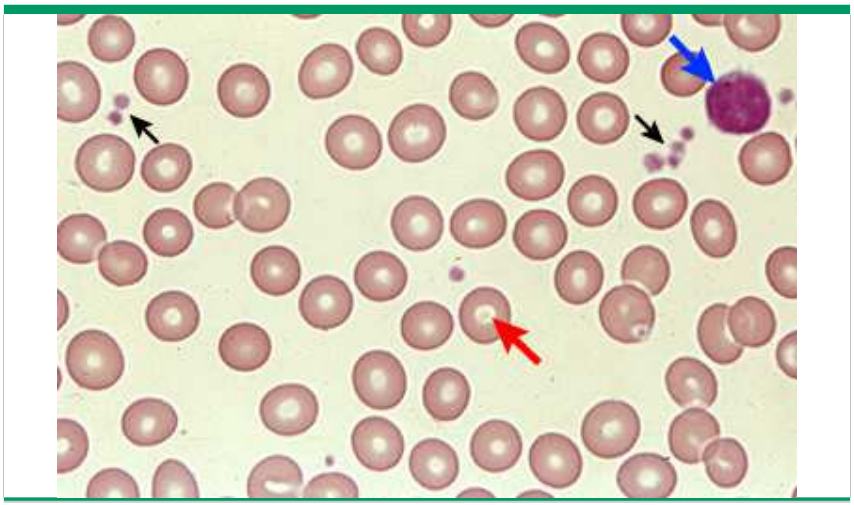


This peripheral blood smear shows platelet clumping (arrows) in an EDTA-anticoagulated blood sample. This patient had an EDTA-dependent platelet agglutinin which caused in vitro platelet clumping, resulting in an artifactually low platelet count (ie, "pseudothrombocytopenia"). No platelet clumping was 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

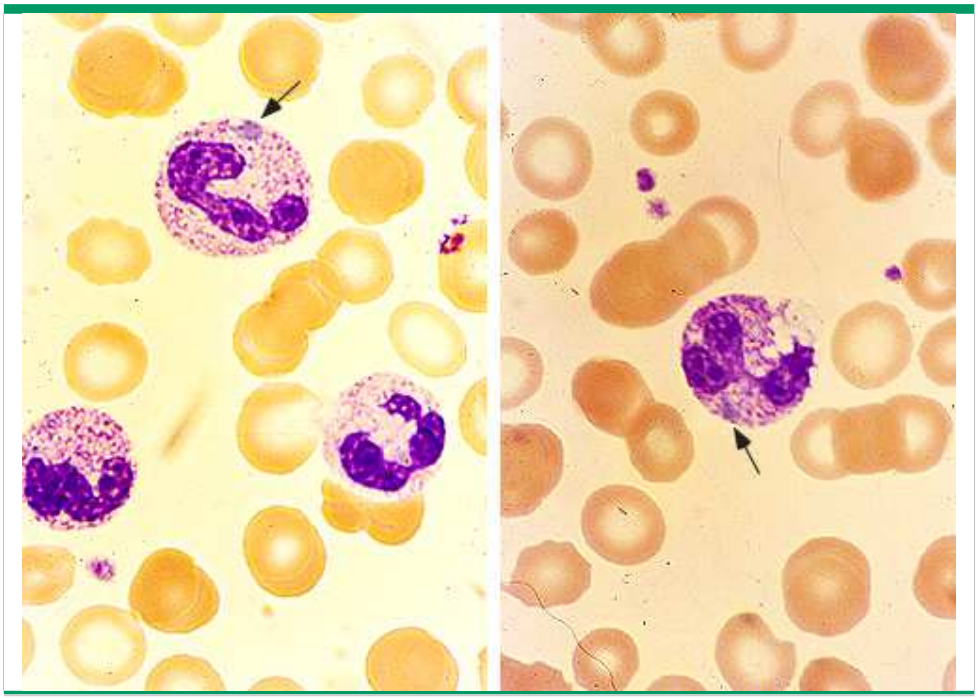


High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central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

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 2.0

Toxic granulations and Döhle bodies in infection/inflammation

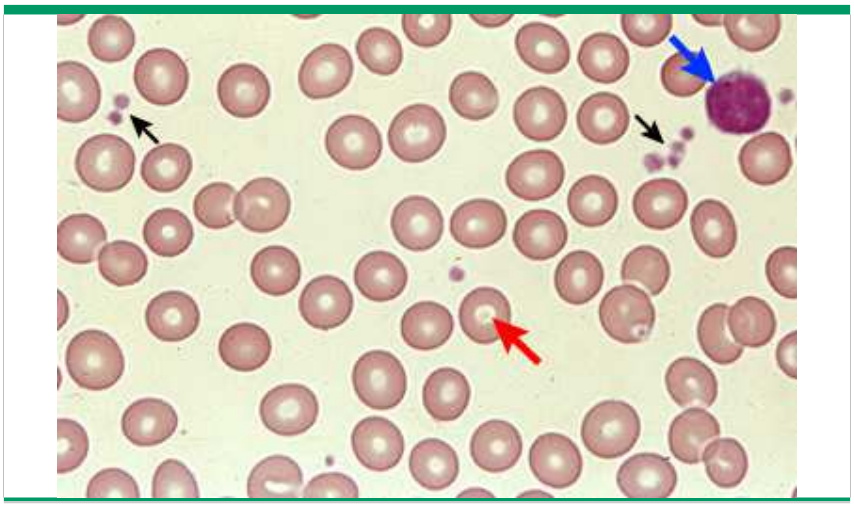


Left panel: Peripheral blood smear shows neutrophils with toxic granulations, which are dark coarse granules. A Döhle body is also seen (arrow). Right panel: A neutrophil with toxic granulations, vacuoles (another toxic change), and a Döhle body (arrow). These abnormalities are characteristic of toxic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

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 70248 Version 2.0

Normal peripheral blood smear

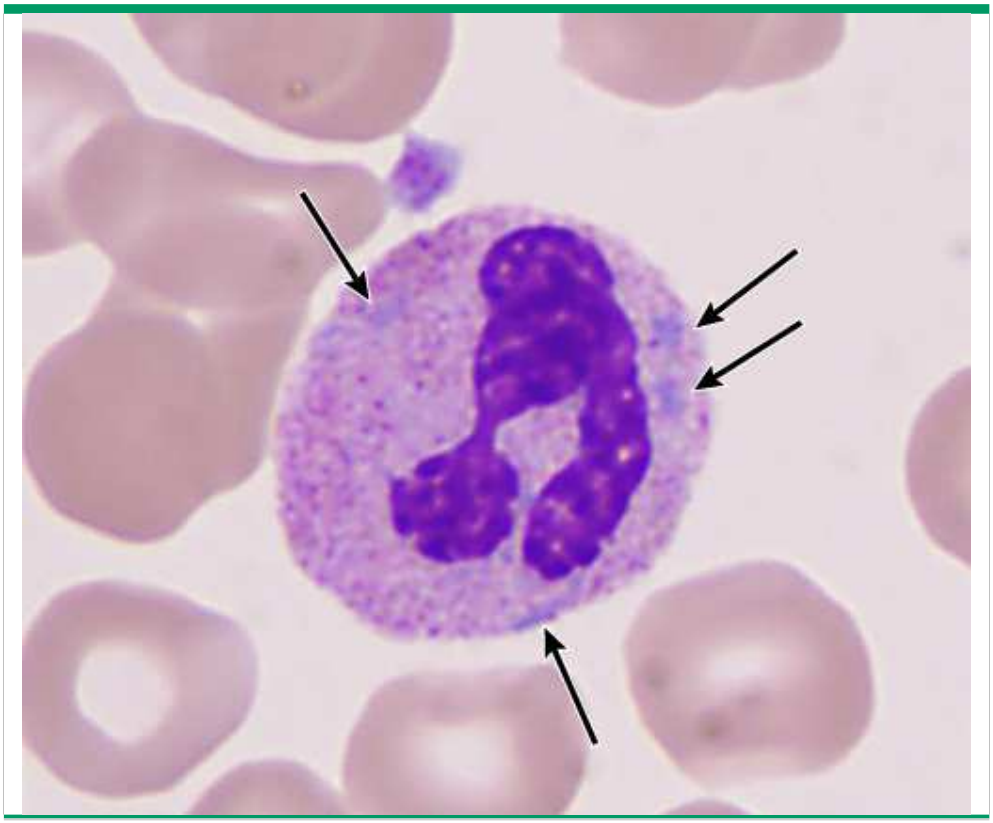


High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central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

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 2.0

Multiple Döhle bodies in a mature neutrophil in a patient with bacterial sepsis

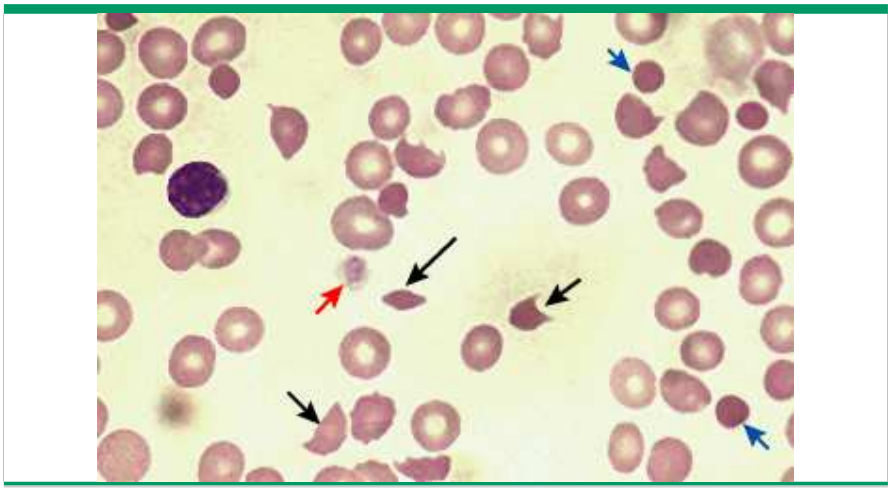


This high power photomicrograph of a peripheral blood smear in a patient with bacterial sepsis shows a mature neutrophil containing multiple Döhle bodies (arrows).

Kindly provided by Dr. German Pihan, Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA.

Graphic 90060 Version 1.0

Peripheral smear in microangiopathic hemolytic anemia showing presence of schistocytes

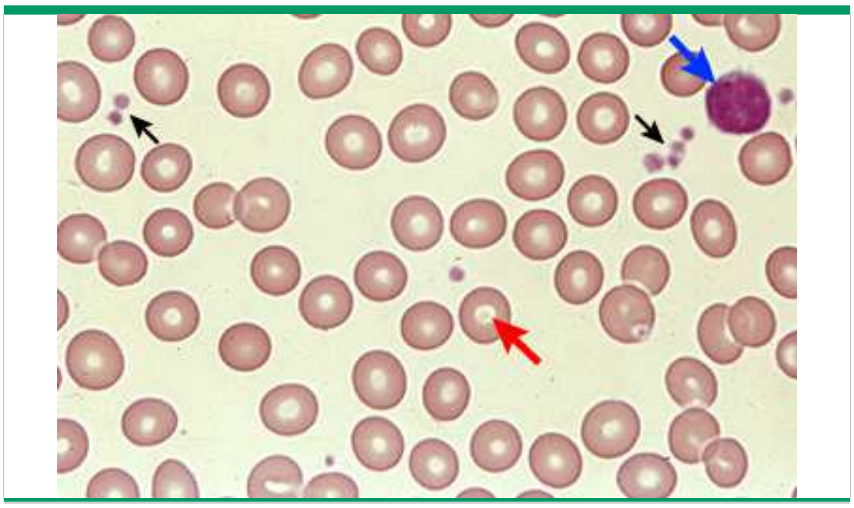


Peripheral blood smear from a patient with a microangiopathic hemolytic anemia with marked red cell fragmentation. The smear shows multiple helmet cells (small black arrows), other fragmented red cells (large black arrow); microspherocytes are also seen (blue arrows). The platelet number is reduced; the large platelet in the center (red arrow) suggests that the thrombocytopenia is due to enhanced destruction.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 70851 Version 6.0

Normal peripheral blood smear

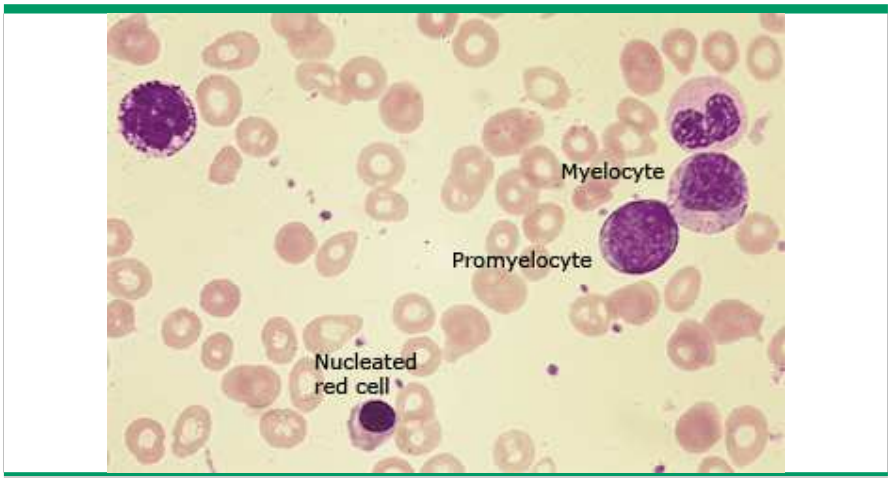


High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central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

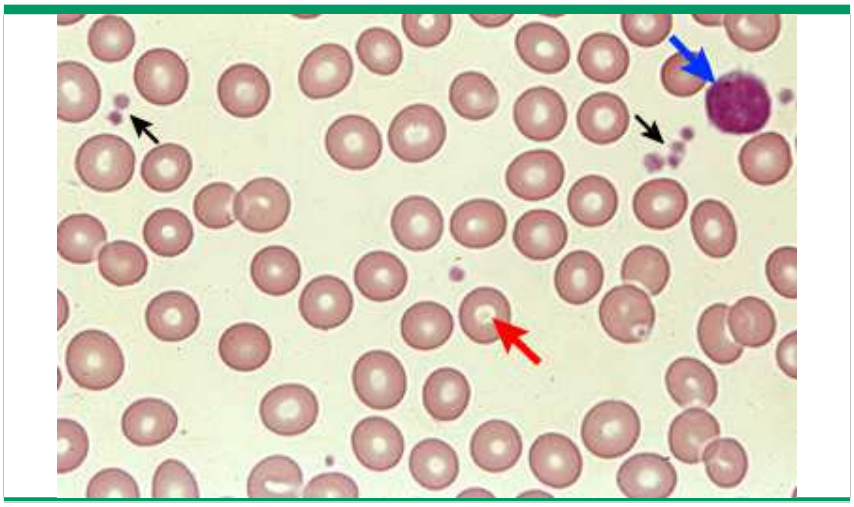


Leukoerythroblastic peripheral blood smear showing the presence of nucleated red cells and immature white cells. This pattern occurs with marrow replacement, usually due to fibrosis that may be idiopathic (eg, primary myelofibrosis) or reactive to conditions such as metastatic cancer.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 68110 Version 3.0

Normal peripheral blood smear

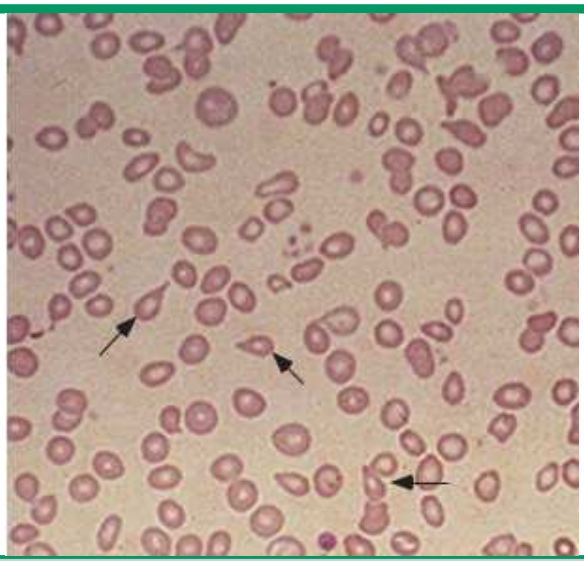


High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central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

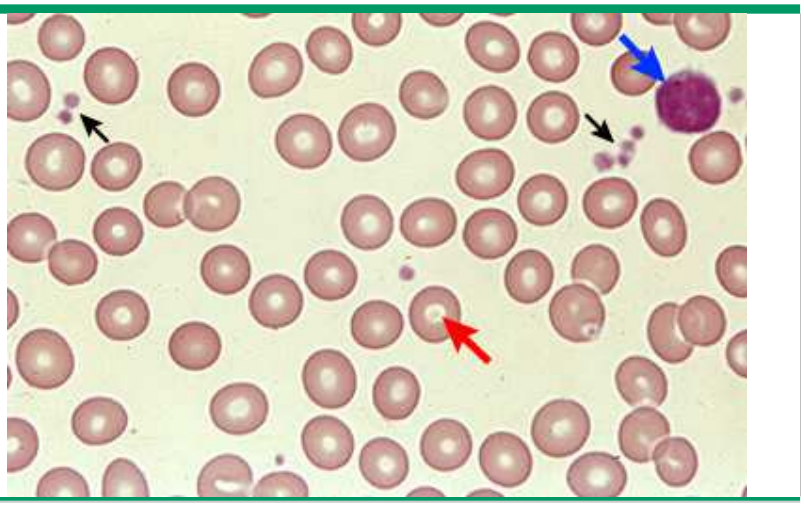


This peripheral smear from a patient with bone marrow fibrosis shows numerous teardrop-shaped red cells (arrows). Note that the teardrops are pointed in several different directions, ruling out an artifact due to preparation of the smear.

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).

Graphic 59683 Version 2.0

Disclosures

Disclosures:**Thomas D Coates, MD** Nothing to disclose. **Donald H Mahoney, Jr, MD** Nothing to disclose. **Laurence A Boxer, MD** Speaker's Bureau: Alexion [PNH (eculizumab)]. Consultant/Advisory Boards: Nora Therapeutics [recurrent spontaneous abortions (G-

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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