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Approach to the adult with pancytopenia

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INTRODUCTION

Pancytopenia refers to decreases in all peripheral blood lineages and is considered to be present when all three cell lines are below the normal reference range.

Pancytopenia can be associated with a multitude of disease states, some of which are life threatening. A thoughtful history and physical examination along with focused laboratory studies are required to establish a diagnosis and select proper management. In most cases of pancytopenia, referral to a hematologist will be important for purposes of diagnosis and/or management.

The diagnostic approach to an adult patient with pancytopenia will be discussed here. The evaluation of isolated neutropenia, anemia, and thrombocytopenia are presented separately. (See "Approach to the adult with unexplained neutropenia" and "Diagnostic approach to anemia in adults" and "Diagnostic approach to thrombocytopenia in adults".)

DEFINITION

Pancytopenia refers to decreases in all peripheral blood lineages. Many disorders that cause pancytopenia can also cause bicytopenia (ie, decreases in only two cell lines); thus, in most cases the evaluation of bicytopenia is similar to that presented here.

Individual laboratories typically establish their own reference ranges for hemoglobin/hematocrit, white blood cell count, and platelet count. These institutional cutoff values supersede published reference standards such as those published by the World Health Organization [1]:

- Red blood cells – Hemoglobin <12 g/dL for non-pregnant women and <13 g/dL for men
- White blood cells – Because neutrophils constitute the majority of leukocytes in the peripheral blood and bone marrow, nearly all cases of low white blood cells (leukopenia) manifest as neutropenia.

  Absolute neutrophil count (ANC) <1800/microL – Calculated as the total white blood cells/microL x (percent [polymorphonuclear cells + bands] ÷ 100) (calculator 1)
- Platelets – Platelet count <150,000/microL

Threshold levels for normal values may differ depending on age, sex, and race [1]. Thresholds may also differ depending on the clinical scenario; as an example, different criteria are used to diagnose certain bone marrow failure syndromes (eg, aplastic anemia, myelodysplastic syndromes). (See "Aplastic anemia: Pathogenesis, clinical manifestations, and diagnosis" and "Prognosis of myelodysplastic neoplasms/syndromes (MDS) in adults".)

MECHANISMS OF PANCYTOPENIA

Hematopoiesis (blood cell production) in the healthy adult takes place in the bone marrow, from which mature blood cells migrate into the circulation, spleen, and other sites. The bone marrow is a dynamic organ and a hematopoietic reservoir that responds to ongoing needs for blood cell production. A balance between blood cell production, distribution in other organs, and ongoing cellular destruction (eg, white blood cells fighting infections, platelet consumption in blood clots, cellular senescence) determines the levels of circulating blood cells [2-5].

Broadly speaking, pancytopenia may be caused by one or more of the following mechanisms:

- Bone marrow infiltration/replacement – Such disorders include hematologic malignancies (eg, leukemia, lymphoma, multiple myeloma, myelodysplastic syndromes), metastatic cancer, myelofibrosis, and infectious diseases (eg, miliary tuberculosis, fungal infections).
- Bone marrow aplasia – Nutritional disorders (eg, deficiencies of vitamin B12 or folate), aplastic anemia, infectious diseases (eg, HIV, viral hepatitis, parvovirus B19), immune destruction, and medications are among the causes of marrow aplasia.
- Blood cell destruction or sequestration – Excessive blood cell destruction occurs in disseminated intravascular coagulation, thrombotic thrombocytopenia purpura, and ineffective hematopoiesis (eg, myelodysplastic syndromes, megaloblastic disorders), while excessive sequestration may be due to hypersplenism (eg, from liver cirrhosis, storage diseases, lymphoma, or autoimmune disorders).

Some diseases may cause pancytopenia by multiple mechanisms. As an example, a lymphoma may infiltrate the bone marrow, cause hypersplenism, induce immune destruction of blood cells, and require treatment with cytotoxic agents. Similarly, Crohn disease may impair absorption of iron, folate, and vitamin B12; induce an inflammatory state that exacerbates anemia; require partial bowel resection that affects absorption of nutrients and calories; and require treatment with myelosuppressive agents.

CAUSES OF PANCYTOPENIA

Examples of causes of pancytopenia are categorized in the table by the predominant mechanism(s) of cytopenia; because some diseases act by more than one mechanism, certain disorders are listed more than once (table 1).

The likely causes of pancytopenia are influenced by geography, socioeconomic conditions, and endemic illnesses. As examples, the likelihood of infectious (eg, malaria, tuberculosis, leishmaniasis) or nutritional causes (eg, folate deficiency) of pancytopenia may be increased in some resource-constrained settings [6,7]. Similarly, the prevalence of human immunodeficiency virus (HIV) infection and alcohol use may influence the likely causes of pancytopenia.

The vast majority of pancytopenia in adults is caused by acquired disorders; rarely, a previously unrecognized inborn error may account for cytopenias that are first detected in adulthood [8]. (See 'Other patient scenarios' below.)

EMERGENCIES

Clinical stabilization is the highest priority for the patient with pancytopenia who is clinically unstable. Immediate hospitalization may be required to control life-threatening infections, provide blood product support, and/or manage other medical emergencies (table 2).

Pancytopenia associated with the following clinical situations will require immediate hematology consultation and/or hospitalization:

- Neutropenia:
  - Absolute neutrophil count (ANC) <1000/microL with fever and/or other evidence of infection or other acute illness. (See "Overview of neutropenic fever syndromes", section on 'Management'.)
  - New diagnosis of moderate or severe neutropenia (ie, ANC <1000/microL and <500/microL, respectively). (See "Approach to the adult with unexplained neutropenia", section on 'Initial evaluation'.)

- Symptomatic anemia (eg, myocardial ischemia, hypotension). (See "Indications and hemoglobin thresholds for red blood cell transfusion in the adult", section on 'Symptomatic patient'.)

- Thrombocytopenia:

  - New finding of platelets <10,000/microL

  - Clinically significant bleeding with platelets <50,000/microL. (See "Diagnostic approach to thrombocytopenia in adults", section on 'Thrombocytopenic emergencies requiring immediate action'.)

- Suspected disseminated intravascular coagulation (DIC), thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), or other thrombotic microangiopathy because of schistocytes on peripheral blood smear accompanied by elevated lactate dehydrogenase. (See "Diagnostic approach to suspected TTP, HUS, or other thrombotic microangiopathy (TMA)".)

- Suspected acute leukemia:

  - New diagnosis (eg, circulating blasts). (See "Evaluation of the peripheral blood smear".)

  - Medical emergencies associated with leukemia (eg, DIC from acute promyelocytic leukemia, tumor lysis syndrome). (See "Evaluation and management of disseminated intravascular coagulation (DIC) in adults", section on 'Diagnostic evaluation' and "Initial treatment of acute promyelocytic leukemia in adults", section on 'Emergency pretreatment evaluation' and "Tumor lysis syndrome: Prevention and treatment", section on 'Hypouricemic agents'.)

- Suspected severe aplastic anemia (ANC <500/microL, platelets <20,000/microL, anemia with reticulocyte count <20,000/microL) or other bone marrow failure syndrome. (See "Aplastic anemia: Pathogenesis, clinical manifestations, and diagnosis", section on 'Evaluation'.)

- Suspected hemophagocytic lymphohistiocytosis (HLH) because of unexplained fever, hepatomegaly, lymphadenopathy, and/or neurologic symptoms in association with very high serum ferritin, liver function abnormalities, and/or coagulopathy. (See "Clinical features and diagnosis of hemophagocytic lymphohistiocytosis", section on 'Clinical features'.)

- Metabolic emergencies in the setting of pancytopenia:

- Hypercalcemia with symptoms (eg, delirium, abdominal pain, dehydration) associated with the cause of pancytopenia (eg, multiple myeloma, metastatic cancer, adult T cell leukemia/lymphoma). (See "Clinical manifestations, pathologic features, and diagnosis of adult T cell leukemia-lymphoma", section on 'Clinical features' and "Treatment of hypercalcemia", section on 'Severe hypercalcemia'.)

- Acute renal failure (eg, hyperkalemia, dehydration, fluid overload) associated with the cause of pancytopenia (eg, multiple myeloma, tumor lysis syndrome). (See "Treatment and prevention of hyperkalemia in adults", section on 'Patients with a hyperkalemic emergency' and "Overview of the management of acute kidney injury (AKI) in adults".)

- Hyperuricemia with renal failure associated with the cause of pancytopenia. (See "Tumor lysis syndrome: Prevention and treatment".)

INITIAL EVALUATION

While there are numerous possible causes of pancytopenia, the differential diagnosis should narrow following an initial history and physical examination, screening laboratory studies, and examination of the peripheral blood smear (table 1). Initial testing should also identify emergency situations and determine the need for (and urgency of) hematology referral (table 2). (See 'Emergencies' above.)

History — Important considerations in the history include:

- **Time course and clinical severity** – Prior laboratory results (when available) and severity and duration of symptoms should be evaluated.

- **Symptoms associated with cytopenias** – Examples include:

  - Recurrent, severe, or unusual infections that may be due to leukopenia/neutropenia

  - Fatigue, dyspnea, chest pain, hemodynamic instability, or claudication due to anemia

  - Bleeding or easy bruising due to thrombocytopenia or disseminated intravascular coagulation

  - Constitutional symptoms, including fevers, night sweats, and/or weight loss

  - Nausea, vomiting, and jaundice that may be associated with liver disease

  Chest pain, hemodynamic instability, severe bleeding, life-threatening infections, and other medical emergencies may require immediate hospitalization for clinical stabilization (table 2).

- **Previous treatments** – Determine if the patient has previously been treated for hematologic disorders, including prior transfusions, hematinics (eg, vitamin B12, folate, iron), or other treatments (eg, apheresis, plasma exchange).

- **Other medical conditions** – Almost any comorbid medical condition or surgical procedure can contribute to or exacerbate cytopenias.

  As an example, a history of Crohn disease is relevant because the inflammatory bowel disease and previous surgeries may affect the patient's nutritional status and impair absorption of essential nutrients and vitamins (eg, iron, folate, vitamin B12), while the inflammatory state may exacerbate anemia, and therapeutic agents may suppress bone marrow function.

- **Problematic medications** – Many medications (including prescription and over-the-counter medications, health supplements, and home or folk remedies) may cause or contribute to cytopenias (table 3).

  The relationship between the onset of pancytopenia and the administration of medications should be defined as much as possible. Some medications (eg, cytotoxic or immunosuppressive agents) cause predictable decreases in blood counts that are generally reversible if the agent is reduced or stopped. Other medications that are not commonly associated with dose-related cytopenias may cause idiosyncratic reactions leading to severe cytopenias. (See 'Suspected medications' below.)

- **Personal and occupational exposures** – Certain personal habits (eg, alcohol consumption, diet), infection history (eg, HIV, viral hepatitides), exposure to toxic agents at work or home (eg, organic solvents), and travel history (eg, exposure to malaria, leishmania) may also be relevant.

Physical findings — The physical examination may provide clues to the underlying etiology, including:

- Rashes that may be related to drug reactions, rheumatologic disorders, infections, and malignancies

- Oral lesions; as examples, thrush suggests immune compromise; oral ulcers may be seen in diseases such as systemic lupus erythematosus

- Lymphadenopathy and/or splenomegaly

- Jaundice and stigmata of liver disease

Laboratory studies — Initial laboratory evaluation should include:

- Complete blood count (CBC), with white blood cell differential count and red blood cell indices
- Examination of the peripheral blood smear, which may reveal abnormalities that would not be detected by automated methods. (See 'Abnormal cells on blood smear' below.)
- Reticulocyte count. An absolute reticulocyte count <20,000 indicates a marked decrease in red blood cell production and suggests a hypoproliferative condition. (See 'Hypoproliferative conditions' below.)
- Prothrombin time (PT) and partial thromboplastin time (PTT). Coagulopathies in the setting of pancytopenia generally require prompt evaluation and referral. (See 'Coagulopathy' below.)
- Serum chemistry tests, including electrolytes, renal and liver function tests, lactate dehydrogenase, calcium, and uric acid. (See 'Metabolic abnormalities' below.)
- Blood type and screen

Hematology referral — Referral to a hematologist for purposes of diagnosis (eg, examination of the peripheral blood smear, bone marrow studies, interpretation of specialized molecular or flow cytometry results) and/or management is nearly always appropriate, unless an etiology is promptly identified that can be readily managed by the non-specialist clinician (eg, vitamin B12 or folate deficiency, alcoholic liver cirrhosis with congestive splenomegaly).

The urgency of referral to a hematologist is influenced by the severity and trajectory of cytopenias, clinical stability, medical complications, and the need for urgent treatment.

- Emergencies – Immediate hematology evaluation should be performed for the emergency situations described above, or in other settings of pancytopenia associated with clinical instability (table 2). (See 'Emergencies' above.)
- Clinical stability – Referral is less urgent (eg, can occur within days to weeks) if the patient is asymptomatic, blood counts are stable and near normal, and there are no medical emergencies. Serial outpatient evaluation of complete blood counts and a review of the peripheral blood smear may be appropriate in select cases of asymptomatic, mild pancytopenia. The case should be discussed with a hematologist if there is uncertainty over the urgency of referral.

SUBSEQUENT EVALUATION

Potential explanations for pancytopenia should emerge from the initial history, physical examination, screening laboratory studies, and review of the peripheral blood smear (table 1).

While a single underlying diagnosis should be sought, more than one potential cause or contributor to pancytopenia may be identified. (See 'Multifactorial causes' below.)

Bone marrow and other specialized evaluation — Bone marrow aspirate and biopsy is useful in many, but not all, patients with pancytopenia. It is especially important in patients for whom a primary hematologic disorder is suspected as the cause of pancytopenia (eg, acute leukemia, aplastic anemia, multiple myeloma) or when the cause of pancytopenia remains elusive after the initial evaluation. The urgency of a bone marrow biopsy is influenced by the likely cause(s) of pancytopenia, as well as the severity and trajectory of cytopenias, clinical stability, medical complications, and the need for urgent treatment, as discussed in sections below. (See 'Specific clinical scenarios' below.)

However, in certain situations, a bone marrow biopsy may be unhelpful or even distracting and confounding. As an example, a bone marrow biopsy performed just days after discontinuation of a suspect medication may show a "maturation arrest" (ie, recovery of bone marrow cells only up to an immature stage of differentiation) that may be morphologically indistinguishable from acute leukemia. Similarly, recent treatment with recombinant hematopoietic growth factors may induce a bone marrow morphology that is indistinguishable from certain myeloproliferative neoplasms or inflammatory conditions. In such situations it may be preferable to delay the biopsy by days to weeks.

Bone marrow biopsies may also be uninformative in some cases when pancytopenia is thought to be due to peripheral blood cell destruction or sequestration (eg, suspected thrombocytopenic purpura, cirrhosis with hypersplenism); clinical evaluation and/or other specialized testing is generally more useful and definitive in such cases.

The hematologist who will perform the procedure should communicate with a laboratory technician and/or pathologist to properly prepare the specimens (eg, place fresh aspirate material in appropriate anticoagulated medium for flow cytometry or molecular studies, and put biopsy specimens in proper fixative), and to order the appropriate tests.

The bone marrow aspirate and biopsy specimens will undergo microscopic examination by a hematopathologist, pathologist, and/or hematologist; review by both the pathologist and involved clinicians can be invaluable in interpreting the bone marrow morphology in the context of the clinical presentation. (See "Bone marrow aspiration and biopsy: Indications and technique" and "Evaluation of bone marrow aspirate smears".)

The differential diagnosis of pancytopenia will inform further specialized testing of the bone marrow and/or peripheral blood (eg, flow cytometry, cytogenetics, molecular studies,

microbiologic cultures). As an example, direct antiglobulin testing and flow cytometry may be needed to confirm the diagnosis of paroxysmal nocturnal hemoglobinuria. Cytogenetic testing (fluorescent in situ hybridization [FISH] or karyotype) of bone marrow or peripheral blood may be required for confirmation of the diagnosis of many hematologic malignancies (eg, leukemias, myelodysplastic syndromes, myeloproliferative neoplasms, lymphomas). Molecular analysis is increasingly important in the diagnosis and risk stratification of many cancers, including hematologic malignancies. (See "General aspects of cytogenetic analysis in hematologic malignancies" and "Personalized medicine", section on 'Cancer treatment'.)

Specific clinical scenarios — Specific clinical scenarios associated with pancytopenia are reviewed in this section.

Coagulopathy — The finding of elevated prothrombin time (PT) and/or partial thromboplastin time (PTT) in the setting of pancytopenia should focus immediate attention on determining if microangiopathic hemolytic anemia (MAHA) is present [9]. This requires urgent examination of the peripheral blood smear by a hematologist or suitably experienced laboratory personnel for the presence of schistocytes with thrombocytopenia. The presence of MAHA may raise the possibility of DIC that may be due to sepsis, acute promyelocytic leukemia, or other causes. (See "Evaluation and management of disseminated intravascular coagulation (DIC) in adults".)

If MAHA is not found, other explanations should be sought for the abnormal PT and/or PTT (eg, liver disease, vitamin K deficiency, medications). This evaluation may require mixing studies and/or specific coagulation factor tests to distinguish the presence of factor inhibitors from effects of medications, liver disease, or vitamin K deficiency. (See "Clinical use of coagulation tests", section on 'Evaluation of abnormal results' and "Clinical features and diagnosis of hemophagocytic lymphohistiocytosis", section on 'Clinical features'.)

Abnormal cells on blood smear — Abnormal cells on the peripheral smear should be examined by an experienced clinician to distinguish hematologic malignancies (eg, leukemia, lymphoma, myelodysplastic syndrome) from other disorders, such as infections (eg, atypical lymphocytes associated with viral or other infections), marrow replacement disorders (eg, myelofibrosis, metastatic cancer, multiple myeloma), and megaloblastic conditions. (See "Evaluation of the peripheral blood smear", section on 'Worrisome findings'.)

Malignant disorders — Examples of abnormal malignant cells on the blood smear of a pancytopenic patient include:

- Circulating blasts associated with leukemia; a substantial proportion of adults with pancytopenia are found to have acute leukemias, hairy cell leukemia, or other hematologic malignancies (picture 1) [7,10-14]. (See "Evaluation of the peripheral blood smear", section on 'Blasts or tumor cells'.)

- Dysplastic leukocytes, including pseudo-Pelger-Huët cells or reduced neutrophil cytoplasmic granules in myelodysplastic syndromes (picture 2 and picture 3). (See "Clinical manifestations, diagnosis, and classification of myelodysplastic syndromes (MDS)", section on 'Blood smear'.)

- Immature myeloid cells, such as promyelocytes, myelocytes, and metamyelocytes that may reflect an underlying myeloproliferative neoplasm (MPN), such as primary myelofibrosis (picture 4). (See "Clinical manifestations and diagnosis of primary myelofibrosis", section on 'Clinical manifestations'.)

- Leukoerythroblastic findings, including nucleated red blood cells associated with myelofibrosis or other MPNs (picture 4). (See "Evaluation of the peripheral blood smear", section on 'Leukoerythroblastic smear'.)

Confirmation of the nature of such abnormal cells will require further specialized testing including:

- Bone marrow aspirate and biopsy

- Flow cytometry of peripheral blood and/or bone marrow

- Cytogenetic testing (fluorescent in situ hybridization [FISH] or karyotype) of bone marrow or peripheral blood

- Molecular studies (eg, mutation analysis, gene expression profiling)

Non-malignant cells — Abnormalities of granulocytes (eg, hypersegmented neutrophils), lymphocytes (eg, atypical lymphocytes associated with viral or other infections), and red blood cells (RBCs) (eg, ovalomacrocytes) may indicate disorders other than hematologic malignancies.

Examples include:

- Hypersegmented neutrophils (ie, five or more nuclear lobes) in association with ovalomacrocytes (ie, enlarged, ovoid RBCs) suggest a megaloblastic disorder (picture 5). (See "Evaluation of the peripheral blood smear", section on 'Lobulation'.)

  The most common causes of these findings are deficiencies of folate and/or vitamin B12. The appearance of the peripheral blood smear is indistinguishable between these two vitamin deficiencies, and establishing the diagnosis requires specific testing. It is important to note that serum folate levels may quickly normalize after feeding a malnourished patient, but RBC folate will more accurately reflect the prior state. (See "Clinical manifestations and diagnosis of vitamin B12 and folate deficiency".)

- Atypical lymphocytes (lymphoid cells with generous and malleable cytoplasm, often indented by surrounding red cells) can be seen during or following viral infections such as infectious mononucleosis, and may be associated with pancytopenia due to bone marrow suppression, hypersplenism, and other mechanisms (picture 6). (See "Evaluation of the peripheral blood smear", section on 'Lymphocytes'.)

- Leukoerythroblastic appearance of the blood smear, with RBC teardrops, nucleated RBCs, and microangiopathic hemolytic anemia (MAHA), may be associated bone marrow infiltration caused by myelofibrosis or metastatic cancer (picture 4). (See "Causes of anemia in patients with cancer", section on 'Overview'.)

- Schistocytes or other evidence of MAHA may reflect disseminated intravascular coagulation, due to sepsis, acute promyelocytic leukemia, or other causes. (See "Evaluation and management of disseminated intravascular coagulation (DIC) in adults".)

Hypoproliferative conditions — Reticulocytopenia (ie, <20,000 reticulocytes/microL) may indicate a hypoproliferative pancytopenia. The urgency and the pace of further evaluation should be influenced by the severity and trajectory of the cytopenias, and the presence of symptoms or complications of the cytopenias. Suspected severe aplastic anemia (absolute neutrophil count [ANC] <500/microL, platelets <20,000/microL), along with reticulocytopenia requires emergency evaluation. (See 'Emergencies' above.)

Other diagnostic considerations include:

- Deficiencies of essential vitamins or minerals (eg, vitamin B12, folate, or copper) [15,16]

- Medications (eg, cytotoxic agents, or idiosyncratic drug reactions) (table 3)

- Bone marrow suppression (eg, alcohol, viral infections)

- Aplastic anemia (eg, autoimmune/idiopathic, which may be associated with paroxysmal nocturnal hemoglobinuria; or associated with drugs, viral infections, or toxins) [17-19]

- Ineffective hematopoiesis (eg, myelodysplastic syndromes, megaloblastic conditions)

- Bone marrow infiltration/replacement (eg, myelofibrosis, metastatic cancer, storage diseases) [20]

- Malignancies associated with immune suppression (eg, hairy cell leukemia, T cell large granular lymphocyte leukemia)

Defining the nature of a hypoproliferative bone marrow condition usually requires testing the following:

- Serum vitamin B12, folate, and/or copper (as appropriate)

If testing for vitamin B12 and folate is unrevealing, and the history does not suggest alcohol, infections, or reactions to medications as a cause of hypoproliferative pancytopenia, further testing may be required:

- Bone marrow aspirate and biopsy, with consideration of immunohistochemical staining, flow cytometry, and other specialized testing.
- Serologic studies to evaluate viral etiologies or autoimmune illnesses (perhaps in concert with specialists in infectious diseases or rheumatology).
- Flow cytometry of peripheral blood (eg, for CD59) may be useful when paroxysmal nocturnal hemoglobinuria (PNH) is associated with aplastic anemia [21]. (See "Clinical manifestations and diagnosis of paroxysmal nocturnal hemoglobinuria", section on 'Diagnosis and classification'.)

Splenomegaly and/or liver disease — The presence of splenomegaly and pancytopenia suggests hypersplenism (ie, sequestration and/or excessive destruction of blood cells in an enlarged spleen). All cell lineages may be affected.

In many, but not all cases, splenomegaly and hypersplenism are associated with liver disease. Conversely, other conditions can cause liver disease and pancytopenia without splenomegaly.

The extent of cytopenias in hypersplenism is variable, but generally less severe than that caused by primary bone marrow disorders. However, splenomegaly and liver disease are associated with many disorders that also contribute to cytopenias by other mechanisms (eg, malignancies, myelofibrosis, infections), and the resultant multifactorial cytopenias may be severe. (See "Splenomegaly and other splenic disorders in adults", section on 'Evaluation (splenomegaly)' and "Approach to the patient with abnormal liver biochemical and function tests", section on 'Initial evaluation'.)

Conditions associated with pancytopenia in the setting of splenomegaly and/or liver disease include:

- Liver disease/cirrhosis and portal hypertension
- Infections (eg, viral infections, malaria, leishmaniasis, endocarditis) [6,22-29]
- Hematologic malignancies (eg, lymphomas, hairy cell leukemia, myeloproliferative neoplasms)
- Extramedullary hematopoiesis (eg, associated with myelofibrosis or thalassemias)
- Congestion (eg, right sided congestive heart failure)

- Inflammation (eg, associated with rheumatoid arthritis [Felty syndrome] or other autoimmune illness, endocarditis)
- Primary splenic disease (eg, hemorrhage, thrombosis)
- Storage diseases (eg, Gaucher disease)
- Hemophagocytic lymphohistiocytosis

The differential diagnosis of pancytopenia in the setting of splenomegaly is influenced by the presence of concurrent lymphadenopathy, constitutional symptoms, stigmata of chronic liver disease, and findings of autoimmune disorders. As examples:

- Presence of both splenomegaly and lymphadenopathy may suggest an underlying hematologic malignancy (eg, lymphoma, leukemia), infectious disease, or autoimmune disorder. (See 'Lymphadenopathy' below.)
- Stigmata of chronic liver disease may suggest pancytopenia caused by hypersplenism from cirrhosis. If no explanation for the underlying liver disease is readily identified, evaluation of the liver by imaging (eg, ultrasound, CT scan) and/or biopsy may be warranted. (See "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Clinical manifestations'.)
- Abnormalities of liver function without stigmata of chronic liver disease or splenomegaly may be associated with infectious diseases (eg, acute viral hepatitis), medications, autoimmune disorders, or hemophagocytic lymphohistiocytosis as potential causes of pancytopenia.

Lymphadenopathy — Detection of lymphadenopathy (localized or generalized) may provide important information regarding the underlying cause of pancytopenia.

Potential disorders associated with lymphadenopathy and pancytopenia include:

- Hematologic malignancies (eg, lymphoma, leukemia)
- Autoimmune illnesses
- Infectious diseases

Aids to the diagnosis of an underlying cause of lymphadenopathy in the setting of pancytopenia include:

- Imaging (eg, CT scan, ultrasound, or PET scan to define the extent of lymphadenopathy, and as a possible adjunct to biopsy)
- Lymph node biopsy (including morphology, flow cytometry, molecular studies)

- Flow cytometry of peripheral blood and/or lymph node specimen (eg, to evaluate for hematologic malignancies)
- Serologic studies for infectious or autoimmune illnesses
- Bone marrow aspirate and biopsy may be required if other studies are non-diagnostic

Evaluation of the patient with lymphadenopathy is discussed separately. (See "Evaluation of peripheral lymphadenopathy in adults".)

Autoimmune conditions — Variable degrees of pancytopenia are commonly seen in patients with previously diagnosed autoimmune illnesses. Rheumatoid arthritis/Felty syndrome, systemic lupus erythematosus, and sarcoidosis are often associated with cytopenias, and some of the treatments for these illnesses (eg, gold salts, cytotoxic agents) may exacerbate the cytopenias. (See "Hematologic complications of rheumatoid arthritis".)

Furthermore, autoimmune diseases are often associated with other conditions that can cause pancytopenia (eg, pernicious anemia, thyroid disease, T cell large granular lymphocyte leukemia [T-LGL]) [30]. Thus, pancytopenia in the setting of autoimmune illnesses is frequently multifactorial. (See "Clinical manifestations and diagnosis of Felty syndrome".)

An important component of the management of cytopenias in the setting of known autoimmune illness is identifying conditions that may be contributing to the cytopenias.

Examples include:

- Associated disorders should be sought and managed (eg, folate deficiency, vitamin B12 deficiency associated with pernicious anemia, autoimmune thyroid disease)
- Alternative therapeutic agents may be considered (in consultation with the clinician managing the autoimmune illness) in an effort to lessen bone marrow suppression and inflammation. (See "Drug therapy in Felty syndrome".)
- Consideration may be given to splenectomy in some patients with symptomatic Felty syndrome. (See "Role of splenectomy for Felty syndrome".)
- If T-LGL is suspected, evaluation by flow cytometry of peripheral blood or bone marrow aspirate/biopsy should be considered. (See "Clinical manifestations, pathologic features, and diagnosis of T cell large granular lymphocyte leukemia", section on 'Pathologic features'.)

In some patients, a "forme fruste" of an autoimmune illness may be suspected, but no firm diagnosis has been established. (See 'Other patient scenarios' below.)

Constitutional symptoms — Pancytopenia may present in the setting of otherwise unexplained fevers, soaking sweats, and weight loss. It may be especially important to consider an infectious etiology or hemophagocytic lymphohistiocytosis in this setting. Possible causes of pancytopenia associated with constitutional symptoms include:

- Infections (viral illness, miliary tuberculosis, fungal infection, endocarditis)
- Hemophagocytic lymphohistiocytosis (HLH)
- Hematologic malignancies (eg, lymphoma, leukemia)
- Autoimmune illnesses

The presence of lymphadenopathy, liver disease, splenomegaly, or other findings can provide important clues to the nature of the underlying illness, and the evaluation in these settings is discussed above. (See 'Splenomegaly and/or liver disease' above and 'Lymphadenopathy' above.)

In some patients, constitutional symptoms may be the only apparent clinical findings. Establishing the diagnosis in such a setting may be challenging. If no likely diagnosis presents itself, and especially if the cytopenias are severe or associated with symptoms and/or complications, a bone marrow aspirate and biopsy with specialized infectious disease evaluation of the bone marrow specimen (eg, fungal and/or mycobacterial cultures and stains) should be performed, as appropriate. Other aspects of the evaluation of patients with otherwise unexplained fever and other constitutional symptoms are discussed separately. (See "Approach to the adult with fever of unknown origin", section on 'Diagnostic approach' and "Evaluation of the patient with night sweats or generalized hyperhidrosis", section on 'Initial assessment of all patients'.)

A high index of suspicion must be maintained for the presence of HLH in the setting of pancytopenia associated with constitutional symptoms but no other clinical findings [31-33]. Diagnosis of HLH is supported by the following (see "Clinical features and diagnosis of hemophagocytic lymphohistiocytosis", section on 'Evaluation and diagnostic testing'):

- Ferritin – Serum ferritin is usually very high (often >5000 ng/mL) and has high specificity in children, but not in adults [34]; however, a ferritin <500 ng/mL has excellent negative predictive value for excluding the diagnosis
- Liver function tests (LFTs) – While not one of the diagnostic criteria for HLH, elevated liver enzymes (AST, ALT, GGT), lactate dehydrogenase (LDH), and bilirubin are elevated in nearly all patients
- Hypofibrinogenemia – This may often be out of proportion to other coagulation parameters

- Triglycerides – Marked elevation of triglycerides is typically seen, especially with severe liver involvement
- Soluble CD25 – Elevated soluble IL-2 receptor alpha (sIL-2R or sCD25)
- NK cell function – Low/absent NK cell function/degranulation by flow cytometry (in children but not adults)
- Bone marrow biopsy – Findings of hemophagocytosis and/or infiltration by activated macrophages
- Organomegaly – Splenomegaly and/or hepatomegaly may be present

Metabolic abnormalities — Certain metabolic disorders (eg, hypercalcemia, tumor lysis syndrome, renal failure, hyperuricemia) may be associated with diseases that also cause pancytopenia, including multiple myeloma, leukemia, and lymphoma [35,36]. The association of these metabolic complications with pancytopenia may constitute a medical emergency, and require urgent hospitalization and/or referral to a hematologist for establishing the diagnosis and initiating prompt management (table 2).

If an underlying diagnosis is known but was not previously associated with pancytopenia, the clinician must investigate causes for the decline in blood counts. The cause(s) will often be multifactorial, but consideration should be given to:

- Review of disease status to assess progressive disease or treatment resistance, including restaging of lymphomas or myeloma (eg, repeat CT or PET-CT scans, serologic evaluation of multiple myeloma)
- Assessment of a fundamental change in the disease (eg, Richter transformation of a previously diagnosed lymphoma, progression of myelodysplastic syndrome to acute leukemia) may require repeat bone marrow or lymph node biopsy
- Complications of treatment (eg, drug-associated bone marrow aplasia, treatment-associated leukemia)

Further evaluation and management of these disorders are discussed separately. (See "Overview of the complications of acute myeloid leukemia", section on 'Tumor lysis syndrome' and "Tumor lysis syndrome: Pathogenesis, clinical manifestations, definition, etiology and risk factors", section on 'Clinical manifestations' and "Multiple myeloma: Clinical features, laboratory manifestations, and diagnosis", section on 'Evaluation'.)

Suspected medications — When a particular medication is suspected as a cause of pancytopenia, consideration should be given to discontinuing that medication (or perhaps reducing the dose) in consultation with other treating clinicians. This decision will be

influenced by the severity of the cytopenias, the trajectory of the blood counts, clinical symptoms, and the reason why the medication is being administered.

For cytotoxic or myelosuppressive agents, blood count recovery can generally be expected within days to weeks. When such drugs are thought to be the cause of pancytopenia, it may be preferable to observe the blood counts for one or two weeks rather than immediately performing a bone marrow biopsy.

When an idiosyncratic reaction is a likely cause of pancytopenia, a response to discontinuing the medication is less predictable and recovery of blood counts may be protracted. The clinical presentation and the appearance of the bone marrow in such situations may be indistinguishable from idiopathic aplastic anemia. The clinician's judgment is needed to distinguish between these diagnostic possibilities, since confirmatory tests are rarely available or conclusive.

An immediate bone marrow biopsy may not be helpful when a medication is suspected to be the cause of pancytopenia. A finding of aplasia or hypoplasia will not confirm the identity or nature of the etiologic agent. Additionally, if a biopsy is performed early in the recovery process, the bone marrow may erroneously suggest an acute leukemia, because the recovering cells may exhibit a "maturation arrest" as hematopoiesis has only progressed to an immature stage of maturation. In such a clinical setting, serial observation of the patient and blood counts may be the most useful diagnostic approach.

Mechanisms of drug-associated cytopenias include allergic reactions that affect bone marrow production and/or increase peripheral destruction, and pseudo-allergic reactions. Allergic reactions may be influenced by the patient's immunologic background (ie, HLA type), comorbid conditions, pharmacogenomic constitution [37], prior exposure to that medication or related drugs, and other clinical features. Exposure to some drugs can induce a hypoproliferative pancytopenia that may be indistinguishable from idiopathic aplastic anemia; recovery of blood counts during a period of observation after discontinuing the suspect medication, if clinically reasonable, may help to distinguish between these diagnoses (table 3). (See "An approach to the patient with drug allergy".)

Multifactorial causes — Often, more than one disorder may contribute to pancytopenia, a so-called multifactorial pancytopenia.

Examples include:

- Alcohol use, folate deficiency, cirrhosis, splenomegaly
- HIV infection, multiple medications, AIDS-associated lymphoma
- Autoimmune disorder, splenomegaly, multiple medications

- Lymphoma with autoimmune cytopenias, cytotoxic medications

Many other such multifactorial clinical pictures are encountered in the evaluation of pancytopenia. In such a setting, it is important to identify reversible or treatable causes of cytopenias. As examples, treatment of vitamin deficiencies, discontinuation of suspect medications, and identification of other treatable conditions should be a high priority in evaluating and managing patients with multifactorial pancytopenia.

Other patient scenarios — The scenarios presented above offer a starting point for the evaluation of pancytopenia in many patients. The pace of diagnostic evaluation will be influenced by the severity and trajectory of the cytopenias and the patient's clinical status (eg, presence of medical emergencies, clinical stability, and associated symptoms).

Relatively stable patients with mild cytopenias may undergo an outpatient diagnostic work-up with serial evaluation of blood counts. If the counts decline, complications of cytopenias develop, and/or the evaluation is unrevealing, bone marrow examination should be considered.

- **Young patient with mild cytopenias** – A younger adult with mild, asymptomatic pancytopenia may have no definitive clinical findings to suggest the cause of the cytopenias. The history may reveal family members with autoimmune conditions, thyroid disease, or pernicious anemia, and the patient may have vague musculoskeletal symptoms, but does not meet diagnostic criteria for an autoimmune disorder. In some such cases, this may represent a "forme fruste" of an autoimmune disorder and the cytopenias may be identified before other manifestations of the disorder. In others, the cytopenias may reflect recovery from a viral infection or reaction to a medication.

  A bone marrow biopsy may not be helpful in this setting, as no diagnostic abnormalities may be identified, unless there is suspicion of an associated immune disorder or lymphoma. Such an asymptomatic patient with mild pancytopenia may have serial outpatient evaluation of complete blood counts and a review of the peripheral blood smear and be counseled about monitoring symptoms; the case should be discussed with a hematologist if there is uncertainty over the urgency of referral.

- **Adult presentation of inborn abnormalities** – Rare patients will present with late onset congenital disorders. The patient may have had mild, longstanding cytopenias that were not evaluated or for which initial diagnostic testing was unrevealing. In some cases, findings that were previously dismissed (eg, premature graying of the hair, abnormalities of fingernails or skeleton) may be related to an underlying congenital abnormality [8]. Monocytopenia, recurrent viral infections, disseminated nontuberculous mycobacterial infections, opportunistic fungal infections, pulmonary alveolar proteinosis, and primary lymphedema may suggest GATA2 deficiency. A family

history of liver cirrhosis or pulmonary fibrosis raises the possibility of a telomere biology disorder. (See "Dyskeratosis congenita and other telomere biology disorders" and "Familial disorders of acute leukemia and myelodysplastic syndromes".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Bone marrow failure syndromes".)

SUMMARY

- **Definitions** – Pancytopenia refers to a decrease in ≥2 blood lineages. (See 'Definition' above.)

  Values may differ among laboratories, but we use the following criteria:

  - **Hemoglobin (Hb)** – Men <13 g/dL; non-pregnant women <12 g/dL
  - **Absolute neutrophil count (ANC)** – ANC <1800/microL (calculator 1)
  - **Platelets** – Platelets <150,000/microL

- **Mechanisms** – Pancytopenia may be caused by bone marrow aplasia, marrow infiltration/replacement, ineffective hematopoiesis, and/or excessive blood cell destruction or sequestration (table 1). (See 'Mechanisms of pancytopenia' above.)

- **Initial evaluation**

  - **Clinical** – History and examination should evaluate the severity, time course, and trajectory of pancytopenia (if available); fatigue, dyspnea, infections, and bleeding/bruising; medications (table 3); toxic exposures; comorbid illnesses; and relevant physical findings (table 3). (See 'Initial evaluation' above.)

  - **Laboratory** (see 'Laboratory studies' above):

    - Complete blood count (CBC) with differential count
    - Reticulocyte count
    - Blood smear
    - Prothrombin time/partial thromboplastin time (PT/PTT)

- Blood type and screen
- Complete metabolic panel

- **Emergencies** – Certain conditions may require urgent diagnostic evaluation, management, and/or hospitalization, including (table 2) (see 'Emergencies' above):
  - **Febrile neutropenia** – Fever or other infectious findings associated with neutropenia
  - **Symptomatic anemia** – Cardiac symptoms, including ischemia, hemodynamic instability, or worsening congestive heart failure
  - **Severe or symptomatic thrombocytopenia** – Platelets <10,000/microL or <50,000/microL in association with bleeding
  - **Abnormal blood smear** – Microangiopathy or blasts on smear
- **Further evaluation**
  - **Clinically stable with mild cytopenias** – For milder cytopenias and no clinical complications, it may be satisfactory to monitor the patient closely over days to a few weeks without immediate diagnostic evaluation. Examples include a recent viral infection, alcohol overuse, myelosuppressive agents and other medications, or suspected folate or vitamin B12 deficiency. (See 'Subsequent evaluation' above.)

    However, further evaluation is needed if blood counts decline, no clinical improvement is observed, and/or complications arise.
  - **Other scenarios** – For patients without a readily explained or reversible cause of cytopenias, diagnostic evaluation with a bone marrow (BM) examination, with or without flow cytometry is needed.

    Examples of specific scenarios include:

    - **Suspected hematologic malignancy** – Circulating blasts or other immature myeloid cells (picture 1), dysplastic features (picture 3 and picture 2), or other clinical findings or laboratory features that suggest an acute leukemia, myelodysplastic syndrome (MDS), lymphoma, or other hematologic malignancy should be evaluated as described separately. (See "Clinical manifestations, pathologic features, and diagnosis of acute myeloid leukemia" and "Clinical manifestations, diagnosis, and classification of myelodysplastic syndromes (MDS)".)

- **Aplastic anemia** – For severe cytopenias without an abnormal blood smear, aplastic anemia should be evaluated with a BM examination, as described separately. (See "Aplastic anemia: Pathogenesis, clinical manifestations, and diagnosis".)

- **Suspected inherited disorder** – An inherited condition should be considered for a patient with unexplained cytopenias, characteristic somatic abnormalities, or such a family history. Evaluation and diagnosis of Fanconi anemia, telomere disorders, and other inherited conditions are described separately. (See "Clinical manifestations and diagnosis of Fanconi anemia" and "Dyskeratosis congenita and other telomere biology disorders".)

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Topic 13938 Version 16.0

GRAPHICS

Causes of pancytopenia (organized by mechanism*)

Acquired

- Bone marrow infiltration/replacement
  - Malignant
    - Acute leukemias
    - Chronic leukemias/myeloproliferative neoplasms (MPN)
    - Myelodysplastic syndromes (MDS)
    - Multiple myeloma
    - Metastatic cancer
  - Non-malignant
    - Myelofibrosis
    - Infectious (eg, fungal, tuberculous)
    - Storage diseases
- Bone marrow failure
  - Immune destruction/suppression
    - Aplastic anemia/paroxysmal nocturnal hemoglobinuria
    - Medications¶
      - Cytotoxic drugs
      - Idiosyncratic reactions to medications
    - Large granular lymphocyte leukemia
    - Autoimmune disorders (eg, systemic lupus erythematosus [SLE], rheumatoid arthritis [RA], sarcoidosis)
    - Hemophagocytic lymphohistiocytosis (HLH)
  - Nutritional
    - Megaloblastic (vitamin B12, folate)
    - Excessive alcohol
    - Other (eg, copper deficiency, zinc toxicity)
    - Malnutrition/anorexia nervosa with gelatinous degeneration
  - Marrow suppression
    - Viral infection (eg, HIV, hepatitis, Epstein-Barr virus [EBV])
  - Ineffective hematopoiesis (eg, MDS, nutritional)
- Destruction/sequestration/redistribution
  - Consumption
    - Disseminated intravascular coagulation (eg, associated with sepsis, acute promyelocytic leukemia)
  - Splenomegaly
    - Portal hypertension/cirrhosis
    - Infections (eg, EBV)
    - Autoimmune disorders (eg, SLE, RA/Felty syndrome)
    - Malignancies (eg, lymphomas, MPN)

- Myelofibrosis with myeloid metaplasia
- Storage diseases (eg, Gaucher)

Congenital

- Wiskott Aldrich syndrome
- Fanconi anemia
- Dyskeratosis congenital/telomere biology disorders
- Shwachman-Diamond syndrome
- GATA2 deficiency
- Hemophagocytic lymphohistiocytosis (HLH)

* Note that some disorders are included in more than one category, as they may cause cytopenias by multiple mechanisms (eg, lymphomas may be associated with bone marrow failure due to marrow replacement, increased sequestration due to splenomegaly, and immune destruction).

¶ Refer to accompanying table of drugs associated with cytopenias.

Graphic 112134 Version 4.0

Emergencies associated with pancytopenia

- Neutropenia (new diagnosis or associated with fever/infection)
- Symptomatic anemia (eg, cardiac ischemia, hemodynamic instability, worsening congestive heart failure)
- Thrombocytopenia (platelets <10,000/microL, or <50,000/microL associated with bleeding)
- Disseminated intravascular coagulation
- Abnormal peripheral blood smear (eg, microangiopathy, blasts)
- Severe aplastic anemia
- Hemophagocytic lymphohistiocytosis
- Metabolic emergencies (eg, symptomatic hypercalcemia, hyperkalemia, tumor lysis syndrome)

Graphic 112135 Version 2.0

Some medications and other substances associated with pancytopenia

Category	Examples
Nonsteroidal anti-inflammatory drugs	▪ Aspirin ▪ Diclofenac ▪ Ibuprofen ▪ Indomethacin ▪ Phenylbutazone* ▪ Salicylates ▪ Sulindac
Anti-gout	▪ Allopurinol ▪ Colchicine
Antimicrobials (including antiviral, antihelmintic, and antimalarial)	▪ Albendazole ▪ Chloramphenicol¶ ▪ Cidofovir ▪ Dapsone ▪ Foscarnet ▪ Ganciclovir ▪ Linezolidᐞ ▪ Quinidine ▪ Quinine ▪ Sulfonamides (eg, sulfamethoxazole, sulfisoxazole) ▪ Zidovudine
Anti-epileptics	▪ Carbamazepine ▪ Fosphenytoin ▪ Felbamate ▪ Levetiracetam ▪ Phenytoin ▪ Phenobarbital ▪ Valproate
Anti-thyroid	▪ Methimazole ▪ Propylthiouracil
Cardiovascular (also refer to diuretics)	▪ Aspirin ▪ Amiodarone ▪ Captopril ▪ Lisinopril ▪ Nifedipine ▪ Quinidine ▪ Ticlopidine*
Chelating	▪ Penicillamine

Diuretics	▪ Acetazolamide ▪ Furosemide ▪ Thiazides
Endocrine	▪ Refer to anti-thyroid above
Immunosuppressant (anti-rejection therapy in solid organ transplantation)	▪ Azathioprine◇
Gastrointestinal (acid suppression)	▪ Cimetidine ▪ Nizatidine
Gastrointestinal (inflammatory bowel disease)	▪ Azathioprine◇ ▪ Mercaptopurine◇ ▪ Mesalamine ▪ Sulfasalazine
Psychiatric	▪ Bupropion ▪ Carbamazepine ▪ Lithium ▪ Valproate
Rheumatologic (also refer to anti-gout)	▪ Azathioprine◇ ▪ Gold sodium thiomalate and other gold salts* ▪ Leflunomide ▪ Methotrexate ▪ Penicillamine ▪ Sulfasalazine
Travel medicine (altitude sickness)	▪ Acetazolamide
Other exposures	▪ Benzene ▪ MDMA (ecstasy) ▪ Glue vapors ▪ Pesticides ▪ Radiation ▪ Solvents, organic

This table does not report all medications that have been associated with pancytopenia. In some cases, the report of an association between a medication and cytopenias does not prove causality. Refer to accompanying text for details.

Directly cytotoxic chemotherapeutic agents are omitted from this list, as myelosuppression is an anticipated effect. However, immune-mediated pancytopenia has been rarely associated with some directly cytotoxic agents (eg, platinum-based chemotherapy).

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* Not available in the United States; may have limited availability in other countries.

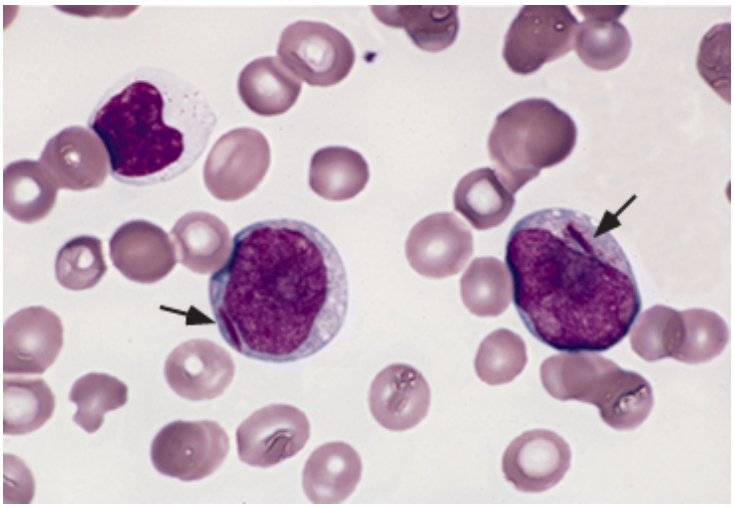
¶ Dose-related reversible bone-marrow suppression is frequently seen with use of chloramphenicol. A rare, non-dose-related form of severe and often fatal aplastic anemia can also occur in about 1 in 20,000 treated patients; as a result, use of chloramphenicol is restricted in many countries. Systemic absorption from ophthalmic use can reportedly occur, but the incidence of serious hematologic toxicity appears to be very low.

Δ Risk factors for linezolid-induced myelosuppression include renal impairment, low baseline blood cell counts, and duration of therapy >14 days.

◇ Azathioprine is a prodrug of mercaptopurine, and both have been associated with aplastic anemia in patients with very low or absent thiopurine methyltransferase (TPMT) enzyme activity. Refer to the UpToDate clinical review of 6-mercaptopurine metabolite monitoring and TPMT testing for additional details.

Graphic 112133 Version 4.0

Myeloblasts with Auer rod in acute myeloid leukemia

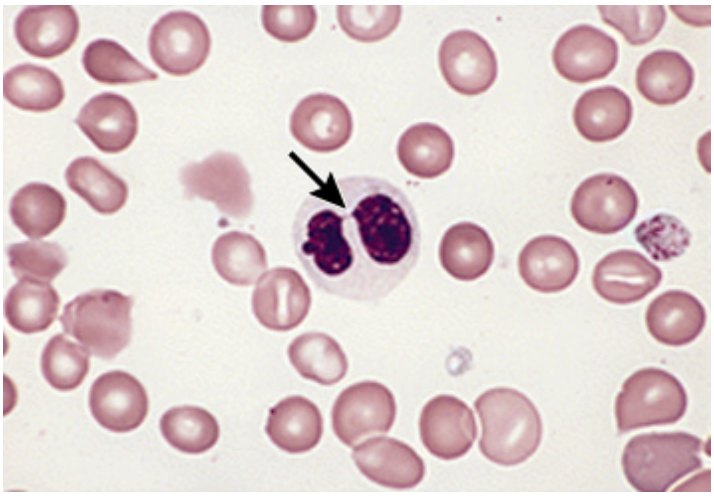


Peripheral smear from a patient with acute myeloid leukemia. There are two myeloblasts, which are large cells with high nuclear-to-cytoplasmic ratio and nucleoli. Each myeloblast has a pink/red rod-like structure (Auer rod) in the cytoplasm (arrows).

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 78291 Version 4.0

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

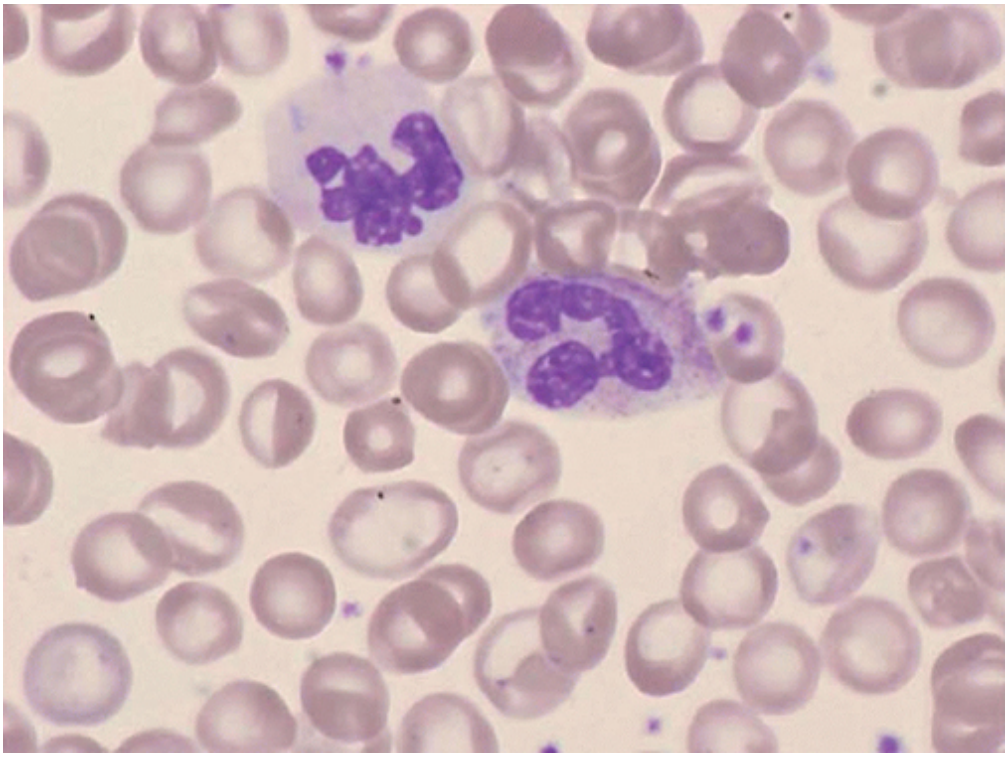


Peripheral blood smear from a patient with refractory anemia with excess blasts (RAEB) shows a neutrophil with a bilobed pseudo-Pelger-Huet (Pelgeroid) nucleus. The two lobes are connected by a thin strand (arrow) giving a "pince-nez" appearance. These nuclei look identical to the those seen in the inherited 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 4.0

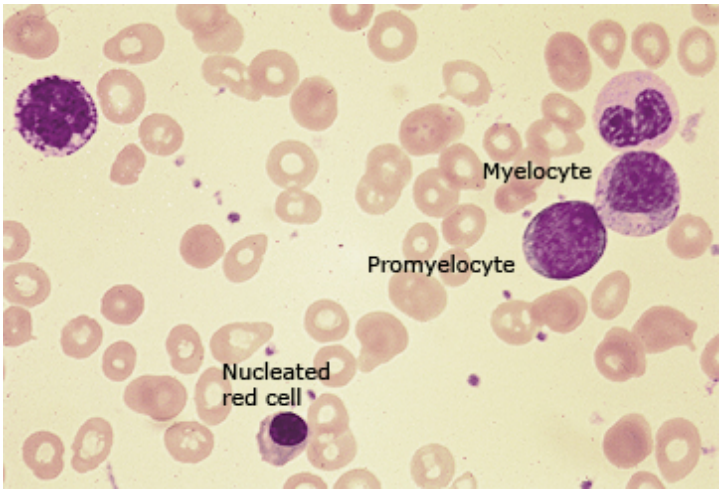
Dysplastic neutrophils in myelodysplastic syndrome



Dysplastic neutrophils, peripheral blood. The cells are nearly agranular. The nuclear segmentation is also abnormal.

Graphic 85881 Version 7.0

Leukoerythroblastic peripheral blood smear

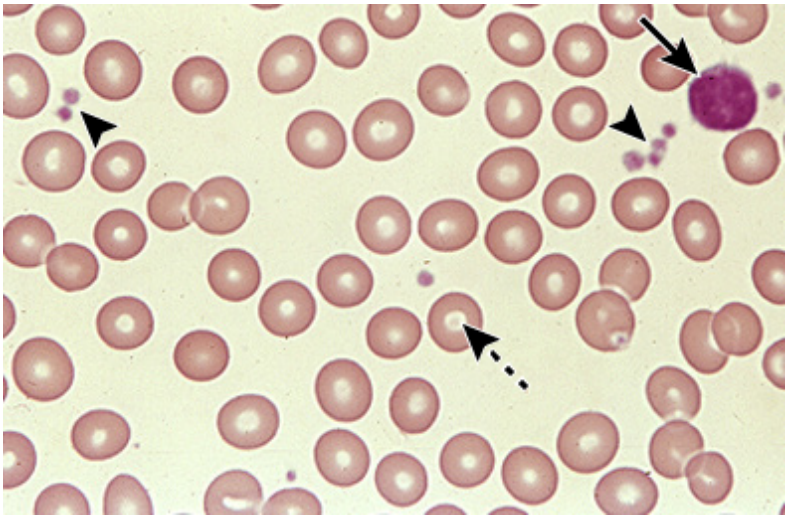


Leukoerythroblastic peripheral blood smear showing the presence of nucleated red cells and immature white cells. This pattern occurs with marrow replacement, usually due to fibrosis that may be idiopathic (eg, primary myelofibrosis) or reactive to conditions such as metastatic cancer.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 68110 Version 3.0

Normal peripheral blood smear

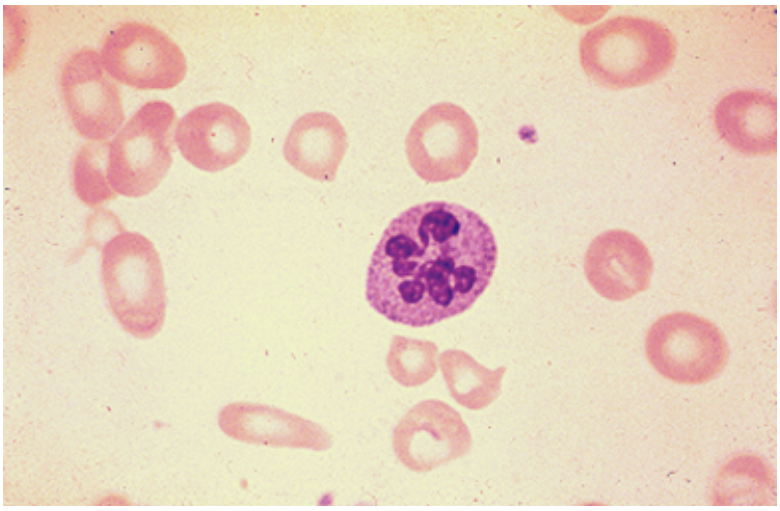


High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor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

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Peripheral blood smear showing megaloblastic changes

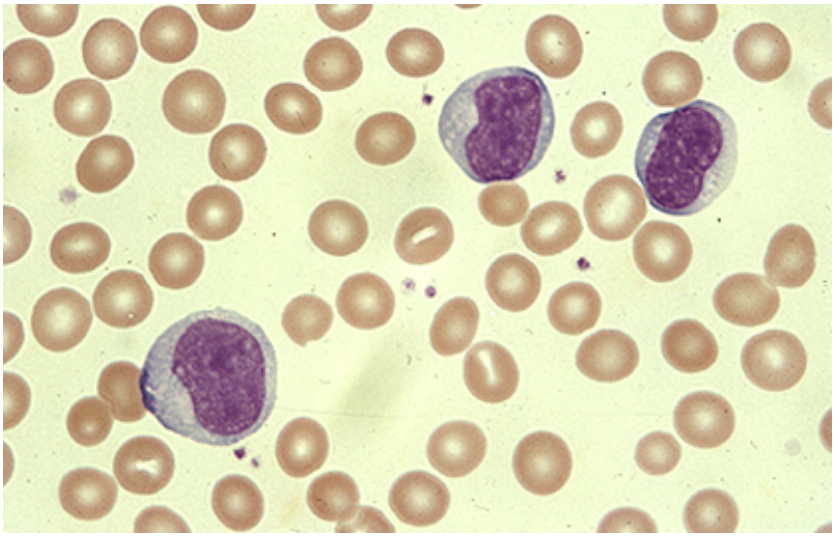


Peripheral blood smear showing a hypersegmented neutrophil (seven lobes) and macroovalocytes, a pattern that can be seen with vitamin B12 (cobalamin) or folate deficiency.

Courtesy of Stanley L Schrier, MD.

Graphic 58820 Version 5.0

Atypical lymphocytes in infectious mononucleosis



Peripheral smear from a patient with infectious mononucleosis shows three atypical lymphocytes with generous cytoplasm.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 55986 Version 2.0

Contributor Disclosures

Nancy Berliner, MD No relevant financial relationship(s) with ineligible companies to disclose. **Peter Newburger, MD** Consultant/Advisory Boards: X4 Pharmaceuticals [neutropenia therapy]. All of the relevant financial relationships listed have been mitigated. **Alan G Rosmarin, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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