

Infectious causes of neutropenia

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INTRODUCTION

Neutropenia can be caused by infection with microorganisms. Conversely, neutropenia can lead to infection, typically from bacterial organisms. A number of different mechanisms are involved, including infection of hematopoietic precursor cells, infection of endothelial cells, increased neutrophil adherence to endothelium, development of antineutrophil antibodies, and enhanced neutrophil utilization at the site of infection associated with hypersplenism. Drugs given to treat these infections may also cause neutropenia. (See "[Drug-induced neutropenia and agranulocytosis](#)".)

This review will discuss the neutropenias that can occur during bacterial, viral, parasitic, or rickettsial infections. Approaches to determining the cause of unexplained neutropenia in children and adults are presented separately. (See "[Evaluation of neutropenia in children and adolescents](#)" and "[Approach to the adult with unexplained neutropenia](#)".)

Infections in patients with neutropenia can range from mild to life-threatening, depending on the cause of the neutropenia. Fever in a neutropenic patient is considered a medical emergency unless the patient is known to be low risk. This issue is discussed separately.

- (See "[Overview of neutropenic fever syndromes](#)".)
- (See "[Children with non-chemotherapy-induced neutropenia and fever: Evaluation](#)".)
- (See "[Children with non-chemotherapy-induced neutropenia and fever: Management](#)".)
- (See "[Risk assessment of adults with chemotherapy-induced neutropenia](#)".)
- (See "[Diagnostic approach to the adult cancer patient with neutropenic fever](#)".)

DEFINITIONS AND INFECTIOUS RISK

Neutropenia is defined as an absolute neutrophil count (ANC) of less than 1500/microL. The 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 differential analysis:

$$\text{ANC} = \text{WBC (cells/microL)} \times \text{percent (PMNs + bands)} \div 100 \text{ ([calculator 1](#))}$$

Neutrophilic metamyelocytes and younger forms are not included in this calculation. The risk of infection begins to increase at an ANC below 1000/microL ([table 1](#)).

Leukopenia and granulocytopenia are generally used interchangeably with neutropenia, although they are somewhat different. Leukopenia refers to a low WBC that may be due to lymphopenia as well as neutropenia, while granulocytopenia refers to a reduced number of granulocytes (neutrophils, eosinophils, and basophils). Agranulocytosis literally means the absence of granulocytes, but the term is often used to indicate severe neutropenia (ie, ANC less than 500/microL).

Most cases of neutropenia are acquired and are due to decreased granulocyte production or increased destruction. Acquired neutropenia is most often due to accelerated turnover, usually resulting from immunologic mechanisms. The key questions that arise in the patient with infection and neutropenia are:

- Is the patient infected because of the neutropenia?
- Is the patient neutropenic because of the infection?
- Are the two events totally unrelated?

The critical clinical question is whether or not the patient is at increased risk of overwhelming infection because of the neutropenia, as this will determine the immediate management of the infection. The propensity to infection from neutropenia is related to the adequacy of the bone marrow reserve pool and other factors such as the presence of vasculitis or immune deficiency. Certain patients with normal marrow reserve and an ANC of zero may be at no increased risk because of the neutropenia. These distinctions are discussed in detail elsewhere. (See "[Evaluation of neutropenia in children and adolescents](#)" and "[Approach to the adult with unexplained neutropenia](#)", section on 'Risk of infection'.)

Neutropenia and leukopenia are commonly associated with infection and are almost always transient [1-3].

VIRAL INFECTION

— Viral infections that can present with neutropenia include human immunodeficiency virus (HIV), infectious mononucleosis, cytomegalovirus (CMV), hepatitis A, and the viral exanthematous diseases. A review of 259 viral infections associated with febrile neutropenia in Vietnamese children reported 50 percent due to influenza A, 31 percent influenza B, 15 percent dengue, measles 1.9 percent, rotavirus 1.5 percent, and Epstein-Barr virus (EBV) 0.4 percent. Only 11 percent had an absolute neutrophil count (ANC) <500/microL [4].

Common childhood viral infections

— Transient mild to moderate neutropenia can be caused by a variety of common viral infections during childhood, including respiratory syncytial virus (RSV), influenza A and B, and parvovirus. In most cases, neutropenia occurs during the first few days of the viral illness and persists for three to eight days [5]. Similar patterns may occur after Epstein-Barr virus (EBV) and human herpes virus 6 (HHV-6) infections, as discussed below.

Coronavirus disease 2019 (COVID-19)

— While infection with CARS-Cov-2 is primarily a respiratory illness, there are significant hematological manifestations and substantial inflammation. Patients usually have leukocytosis at the onset [6]. However, there have been several cases of associated aplastic anemia and/or transient neutropenia [7]. Leukopenia occurs in 17 to 33 percent of patients, but it is primarily due to lymphopenia [8]. Bone marrow aspirates in two cases of neutropenia during COVID showed normal cellularity [7,9]. Severe neutropenia appears to be a relatively uncommon manifestation of COVID-19. (See "COVID-19: Clinical features", section on 'Laboratory findings'.)

HIV

— A variety of hematologic abnormalities are associated with infection by HIV. Anemia, neutropenia, and thrombocytopenia are seen with increasing prevalence as the disease becomes more severe [10-12]. Neutropenia is seen in approximately 40 percent of patients with AIDS [13] either on an autoimmune basis [14] or as a side effect of drug therapy [15]. Lymphopenia occurs in 75 percent of patients due primarily to the fall in the CD4 cell count [13]. (See "Drug-induced neutropenia and agranulocytosis".)

There is a significantly higher risk of hospitalization for bacterial infection among HIV-infected patients with neutropenia, as illustrated by the following observations:

- In one series of 2047 patients, the risk for developing a bacterial infection requiring hospitalization occurred at absolute neutrophil counts (ANCs) below 750/microL and increased progressively as the ANC fell below this level (figure 1) [11].
- In a case-controlled study, the adjusted relative risk for the occurrence of bacterial infection was 2.3 for patients with an ANC below 1000/microL and 7.9 for those with an ANC below 500/microL [12]. The incidence of severe infection was 3 to 5 per 100 patient-months at an ANC below 500/microL.

Increasing the ANC by the administration of granulocyte colony-stimulating factor (G-CSF; filgrastim) or granulocyte-monocyte colony-stimulating factor (GM-CSF; sargramostim) reduces the incidence of infection in patients with advanced HIV disease [16-18]. As an example, a multicenter trial randomized 258 HIV-infected patients with a CD4 cell count below 200/microL and an ANC between 750 and 1000/microL to placebo or increasing doses of daily or intermittent filgrastim to maintain an ANC between 2000 and 10,000/microL [17]. The incidence of severe neutropenia or death was much lower in the treated patients (10 versus 34 percent) who also had 31 percent fewer bacterial infections.

Epstein-Barr virus

— EBV infection produces an acute sporadic infection called infectious mononucleosis (IM) that usually affects young adults. Clinical manifestations of IM include fever, severe pharyngitis, adenopathy, and splenomegaly.

EBV infects B lymphocytes resulting in peripheral blood lymphocytosis with many "atypical" lymphocytes and antibodies against heterologous red cells and EBV. Antineutrophil antibodies may be seen during acute IM, resulting in either a transient PMN aggregation or severe neutropenia [19,20]; the latter is more common in children [21].

Cytomegalovirus

— CMV infection produces fever, sore throat, adenopathy, splenomegaly, and myalgias in otherwise healthy individuals. It is also a major cause of morbidity and mortality in patients with AIDS and in hematopoietic stem cell or solid organ transplant recipients. The blood picture resembles IM except for the absence of IM-associated antibodies. Neutropenia is not part of uncomplicated CMV infection but can occur after the administration of ganciclovir or in disseminated disease in immunosuppressed patients [22-24].

Hepatitis virus group

— Hepatitis A virus infection is associated with transient neutropenia and lymphopenia that usually occur during the second week of illness [25]. The hematologic manifestations can be severe and are independent of the severity of liver disease. Agranulocytosis has been described [26].

Neutropenia can be seen in patients with chronic hepatitis B or C infection. It is usually related to the development of cirrhosis and hypersplenism, or treatment with interferon alfa [27,28].

Aplastic anemia is a rare complication of hepatitis, but it may account for 2 to 5 percent of cases of aplastic anemia in the West [29,30]. The mechanism may involve T cell activation with release of cytokines. The disease most often affects boys and young adult males, with aplasia developing two to three months after an episode of acute

hepatitis [29]. The responsible virus has not been identified; neither hepatitis A, B, C, nor G appears to be involved [29,31]. (See "Acquired aplastic anemia: Pathogenesis, clinical manifestations, and diagnosis".)

Human herpesvirus 6

— HHV-6 infection can cause leukopenia in association with roseola infantum in children or after organ transplantation [32,33]. In one report of four liver transplant recipients, severe cytopenia was seen in all patients, with leukopenia being most prominent (mean 1400/microL) [33].

Viral exanthematous diseases

— Leukopenia and mild neutropenia and lymphopenia are common in infections with measles, rubella, and varicella.

Measles

— During the incubation period in measles, there may be leukocytosis with a white blood cell count of 14,000 to 19,000/microL lasting three days before the onset of fever. This is followed by leukopenia during the week of cough, coryza, conjunctivitis, Koplik spots, and rash [34]. The mean ANC varies widely from 2000 to 8000/microL during the incubation period and falls to less than 500 to 5000/microL, with the nadir occurring at the onset of the rash (figure 2).

Measles virus antigen is localized in circulating neutrophils [35] and neutrophil functions of chemotaxis and bacterial killing are impaired during active infection [36-38]. (See "Laboratory evaluation of neutrophil disorders".)

Live measles virus vaccine also results in transient decrease in white blood cell count from day 3 to day 16 after vaccination. Mild neutropenia is evident by day 8 when low grade fever occurs and returns to baseline two weeks after vaccination [39].

Rubella

— Neutropenia occurs in one-third to one-half of patients with rubella and slowly recedes over six weeks [40]. Changes in lymphocyte count are variable, ranging from lymphocytosis to, less often, lymphopenia.

Varicella

— Varicella infection is usually associated with mild leukocytosis and neutrophilia [41]. However, profound leukopenia and neutropenia of less than 1000/microL with an associated increase in band forms has been described [42].

Other

— Neutropenia can occur during the course of a number of other viral infections. These include:

- Dengue fever virus, in which leukopenia, thrombocytopenia, and a hemorrhagic diathesis are the typical hematologic findings; a low white blood cell count is apparent early in the illness, reaching a nadir after seven days of fever and then returning to normal by the end of two weeks [43,44]. A direct action of dengue virus on the bone marrow is thought to be responsible. (See "Dengue virus infection: Pathogenesis".)
- Colorado tick fever virus, in which leukopenia (1800 to 3400/microL) is the major laboratory finding [45]. The differential shows increased band forms and occasional metamyelocytes and myelocytes, and bone marrow examination reveals depletion of the normal reserve of neutrophils, so-called "myeloid arrest." The virus infects human bone marrow hematopoietic progenitor cells, and the leukopenia is thought to reflect a direct toxic action on the marrow [46,47].
- Yellow fever, in which neutropenia occurs during the first week of infection.
- Phlebotomus fever virus, in which an initial leukopenia is followed by a protracted neutropenia [48,49].

BACTERIAL INFECTION

— Leukocytosis with an increased number of band forms (ie, a shift to the left) is the usual response to bacterial infection. Certain infections, however, such as typhoid fever, *Shigella* enteritis, brucellosis, tularemia, and tuberculosis, are often associated with neutropenia.

Typhoid fever

— Typhoid fever is a severe systemic illness characterized by sustained fever and abdominal symptoms. Leukopenia with neutropenia and an increased percentage of band forms is seen in approximately 25 to 50 percent of adults with this disorder [50]. Thrombocytopenia and anemia are even more frequent, while pancytopenia is found in less than 10 percent of cases [51].

Several consequences of infection in the early phase of the disease contribute to the neutropenia:

- The bone marrow shows granulocytic hyperplasia with hemophagocytosis followed by granuloma in the later phases [52,53]. Hemophagocytosis, if extensive, contributes to peripheral blood cytopenia [54]. (See "Enteric (typhoid and paratyphoid) fever: Epidemiology, clinical manifestations, and diagnosis".)
- Plasma concentrations of endotoxin, tumor necrosis factor (TNF)-receptors, interleukin (IL)-6, and interferon-gamma, blood leukocyte expression of TNF-alpha and IL-1 beta genes, and extracellular phospholipase A2 are elevated. These mediators of inflammation up-regulate expression of vascular endothelial cell adhesion molecules and shift circulating PMNs onto sticky endothelium [55-59].

Shigella enteritis

— The white blood cell (WBC) count varies widely from leukopenia to leukocytosis in both children and adults with *Shigella* enteritis, but a striking shift to the left (increased percentage of band forms) is a common feature that helps to distinguish this disorder from *Salmonella* infection or viral enteritis [60,61].

The mechanism by which *Shigella* infection causes neutropenia is not well understood. The outer membrane proteins from two antigenically different strains of *Shigella* (*Shigella flexneri* and *Shigella sonnei*) caused fever and leukopenia followed by transient leukocytosis when injected intravenously into rabbits [62].

Shigellosis can be associated with a number of systemic complications such as septicemia, hemolytic-uremic syndrome, and a leukemoid reaction (see "*Shigella* infection: Epidemiology, clinical manifestations, and diagnosis"). Polymorphonuclear cells (PMNs) from children with complicated Shigellosis are more likely to be activated (as determined by in vitro testing) than PMNs from children with uncomplicated Shigellosis [63]. (See "*Laboratory evaluation of neutrophil disorders*".)

Brucellosis

— Neutropenia occurs in 20 to 30 percent of adults and children with brucellosis [64-66]. Most of these patients are anemic and up to 20 percent are pancytopenic [65,67].

Hypersplenism, hemophagocytosis by marrow macrophages (which correlates with hypersplenism), and granulomatous lesions of the bone marrow appear to contribute to the development of these abnormalities [67-69]. *Brucella melitensis* can almost always be cultured from the bone marrow during the acute stage of the infection [68]. In addition, in one report of 16 patients with pancytopenia who underwent bone marrow biopsy, noncaseating granulomas were present in eleven [67].

Intravenous injection of mice with *Brucella abortus* results in a similar type of chronic infection with splenomegaly characterized by massive numbers of macrophages [70]. Cases of reactive hemophagocytosis with clinical features of fever, wasting, splenomegaly, and pancytopenia have been associated with Brucellosis [71].

Tularemia

— Tularemia is a zoonosis caused by the Gram negative, facultative intracellular coccobacillus, Francisella tularensis. Clinical manifestations are varied and include ulceroglandular disease and pneumonia (see "*Tularemia: Clinical manifestations, diagnosis, treatment, and prevention*"). The mean WBC and differential are usually normal, as neutropenia occurs in only a small percentage of patients [72,73].

PMNs are essential for host defense against primary infection in tularemia. Mice rendered agranulocytic by treatment with a granulocyte-specific antibody and then infected with *Francisella tularensis* became lethally infected in their lungs, liver, and spleen [74].

Tuberculosis

— Hematologic abnormalities are common in patients with hematogenously disseminated miliary tuberculosis. In one study of 109 such patients, the WBC was less than 4000/microL in 15 percent, and 87 percent were lymphopenic with absolute lymphocyte counts less than 1500/microL. Neutropenia was seen as part of pancytopenia in six patients [75]. In another series of 380 patients with pulmonary tuberculosis, leukopenia with neutropenia and lymphopenia was observed in 16 percent of those with very severe disease [76].

RICKETTSIAL INFECTION

—

Neutropenia is common in rickettsialpox and human granulocytic anaplasmosis; it is also seen in severe cases of Rocky Mountain spotted fever.

Rickettsialpox

— Leukopenia occurs in approximately 75 percent of patients with rickettsialpox [77]. Although the differential count is usually normal, there is a relative lymphocytosis in some patients and a left shift of band forms in others. (See "*Rickettsialpox*".)

Human granulocytic anaplasmosis

— Human granulocytic anaplasmosis (HGA; previously called human granulocytic ehrlichiosis) is a rickettsial infection transmitted by tick bite. The vector is *Ixodes scapularis*, which is also the vector for Lyme disease. The spectrum of clinical presentations is wide, and symptoms may be nonspecific. The organism infects neutrophils, which are unable to kill it following internalization; monocytes appear to be resistant [78,79]. Neutropenia and/or lymphopenia are often seen; thrombocytopenia is also common [80,81]. (See "*Human ehrlichiosis and anaplasmosis*", section on 'Human granulocytic anaplasmosis' and "*Biology of Anaplasmataceae*".)

Rocky Mountain spotted fever

— Most cases of Rocky Mountain spotted fever (RMSF) are associated with a normal white blood cell count or leukocytosis [82]. However, leukopenia and neutropenia can occur in patients with severe disease associated with occlusive fibrin microthrombosis, shock, and multiple organ failure. (See "*Epidemiology, clinical manifestations, and diagnosis of Rocky Mountain spotted fever*".)

PARASITIC INFESTATION

Kala-azar and malaria are two parasitic infections with characteristic neutropenia.

Kala-azar

— Infection with *Leishmania donovani* causes fever, hepatosplenomegaly, and neutropenia as part of pancytopenia. All patients have anemia and approximately 43 percent later develop neutropenia. The disease occurs in individuals who have resided in endemic areas (Mediterranean countries, India, East Africa, South America). There is also a hemolytic anemia that may in part be due to the generation of oxidative metabolic products. (See "[Non-immune \(Coombs-negative\) hemolytic anemias in adults](#)".)

Several mechanisms contribute to the neutropenia. Leukokinetic studies on two patients with kala-azar found that the polymorphonuclear cell (PMN) half-life was reduced with shifts of circulating PMNs to pooling and destruction in an enlarged spleen and, to a lesser extent, in the liver [83]. (See "[Approach to the adult with unexplained neutropenia](#)", [section on 'Mechanisms'](#).)

While the bone marrow reserve of PMNs has been noted to be markedly reduced in some [83], in general the marrow shows myeloid hyperplasia and increased megakaryocytes [84]. Rapid destruction of antibody-coated blood cells could contribute to the pancytopenia. Immunologic studies of the pancytopenia in one series revealed membrane-associated antiplatelet, antineutrophil, and antierythrocyte IgG antibodies [85].

The size of the spleen, hemoglobin level, platelet level and number of bone marrow plasma cells are related to the parasite load. The degree of parasitization, spleen size, and duration of illness generally correlate with the severity of the pancytopenia [86]. Amastigote forms of *Leishmania donovani* are found in bone marrow macrophages, PMNs, and eosinophils in 60 to 85 percent of cases [87] but the yield is close to 100 percent if the bone marrow aspirate is cultured and then evaluated [88]. A likely contributor to the anemia is hyperactive bone marrow macrophages which phagocytose immature erythroblasts and cause ineffective erythropoiesis [84,89].

The marked leukopenia in visceral leishmaniasis contributes to secondary infections. Susceptibility to secondary infection can be significantly reduced by treatment with recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF). The effects of GM-CSF on neutropenia and the rate of infection were evaluated in 24 patients with an absolute neutrophil count (ANC) less than 1500/microL [90]. Patients treated with GM-CSF for 10 days, with pentavalent antimony given daily for 20 days, experienced a three- to fourfold increase in ANC at day 5 and 10, respectively. The incidence of secondary infection was reduced in the patients randomly assigned to treatment with to GM-CSF (21 versus 80 percent with placebo). Importantly, all patients, regardless of treatment, had complete resolution of leishmaniasis at three months.

Malaria

— Mild neutropenia is common in malarial infection, although neutrophilia occurs in severe disease. The hyperreactive malarial splenomegaly syndrome (also called the tropical splenomegaly syndrome) occurs throughout Africa, India, and Southeast Asia. It is associated with massive splenomegaly, pancytopenia, high levels of malarial antibodies, and hyper-IgM syndrome, which resolves after prolonged antimalarial therapy [91]. In one series, neutropenia was seen in 7 percent of patients on admission; individuals who developed severe neutropenia were more likely to do so later during the hospitalization than at presentation [92].

The mechanism of the neutropenia has been studied in six subjects with untreated malaria due to *Plasmodium vivax* and a mean ANC of 1700/microL; all had moderate splenomegaly [93]. The number of circulating band forms was increased, the PMN half-life was prolonged, and the total blood granulocyte pool was normal or increased. The marginating PMN pool was greatly enlarged while the circulating PMN pool was reduced, indicating that the apparent neutropenia was due to a shift of circulating PMN into the marginating pool primarily in the spleen and lung. These patients had decreased numbers and reserves of bone marrow PMNs, presumably due to their premature release into the circulation. (See "[Approach to the adult with unexplained neutropenia](#)", [section on 'Mechanisms'](#).)

There is some evidence that sequestration of CD11a-bearing PMNs, due to tumor necrosis factor-induced upregulation of the endothelial expression of intercellular adhesion molecule (ICAM)-1, contributes to the mortality and microvascular lesions with severe malaria. In an experimental model in which mice were infected with murine malaria, the administration of a monoclonal antibody against PMN induced profound neutropenia, abolished PMN sequestration in the lung, and prevented mortality [94].

HEMOPHAGOCYTIC SYNDROME SECONDARY TO INFECTION

Hemophagocytic lymphohistiocytosis (HLH) is a severe, potentially life-threatening syndrome of excess immune activation that can be triggered by numerous viral, bacterial, parasitic, and fungal infections. Epstein-Barr virus, cytomegalovirus, parvovirus, and herpes simplex virus are infections that are most often associated with severe forms of HLH, especially in association with genetic variants of genes that involve immune regulation. HLH is discussed in detail separately. (See "[Clinical features and diagnosis of hemophagocytic lymphohistiocytosis](#)", [section on 'Infections'](#).)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basic topics (see "Patient education: Neutropenia (The Basics)")

SUMMARY

- **Description** – Neutropenia is defined as an absolute neutrophil count (ANC) <1500/microL (calculator 1). (See 'Definitions and infectious risk' above.)

There is nothing diagnostically specific about the presence of neutropenia in response to infection. The first question to be answered is: "Is the infection due to the neutropenia, or is the neutropenia from the infection?" The differential diagnosis and approach to evaluation of neutropenia is discussed separately. (See "Evaluation of neutropenia in children and adolescents" and "Approach to the adult with unexplained neutropenia".)

- **Viral infection** – Neutropenia can be seen in a large number of viral infections. The mechanisms differ widely, and include antineutrophil antibodies, hypersplenism, infection-induced bone marrow suppression or aplasia, and toxicity of the drugs used to fight the infection. (See 'Viral infection' above.)
- **Bacterial infections** – Leukocytosis with an increased number of band forms (ie, a shift to the left) is the usual response to bacterial infection. Certain infections, such as typhoid fever, *Shigella* enteritis, brucellosis, tularemia, and tuberculosis, are often associated with neutropenia. Hypersplenism, hemophagocytosis by marrow macrophages, and granulomatous lesions of the bone marrow contribute to the development of these abnormalities. (See 'Bacterial infection' above.)
- **Rickettsial infection** – Neutropenia is common in rickettsialpox and human granulocytic anaplasmosis (previously called human granulocytic ehrlichiosis) and is also seen in severe cases of Rocky Mountain spotted fever. Peripheral destruction appears to be the most common mechanism. (See 'Rickettsial infection' above.)
- **Parasitic infestation** – Both kala-azar and malaria can be associated with neutropenia, often secondary to sequestration of neutrophils within an enlarged spleen. (See 'Parasitic infestation' above.)
- **Hemophagocytic syndrome** – Neutropenia (with or without other cytopenias) can occur in the setting of hemophagocytic lymphohistiocytosis (HLH), which is often triggered by an acute infection. (See "Clinical features and diagnosis of hemophagocytic lymphohistiocytosis".)

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