INTRODUCTION — This topic review will provide an overview of the causes, clinical manifestations, diagnosis, and management of neutropenia when it occurs as an isolated or predominant feature. Neutropenia is also a common manifestation of bone marrow defects associated with reductions in red cells and platelets, such as aplastic anemia, leukemia, myelodysplasia, megaloblastic anemia due to vitamin B12 or folate deficiency, and the administration of chemotherapy. These disorders are reviewed separately.

Laboratory evaluation of neutropenia and neutrophil function, as well as various disorders associated with neutropenia are discussed separately. (See "Laboratory evaluation of neutropenia and neutrophil dysfunction" and "Congenital neutropenia" and "Cyclic neutropenia" and "Primary immune neutropenia" and "Neutropenia associated with infections" and "Drug-induced neutropenia and agranulocytosis" and "Hematologic manifestations of HIV infection: Neutropenia".)

DEFINITIONS — The absolute neutrophil count (ANC) is equal to the product of the white blood cell count (WBC) and the fraction of polymorphonuclear cells (PMNs) and band forms noted on the differential analysis:

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

Neutrophilic metamyelocytes and younger forms are not included in this calculation (calculator 1). An ANC <1500/microL (<1.5 x 10\(^9\))/L) is the generally accepted definition of neutropenia, as well as the threshold for neutrophil toxicity and infectious risk following chemotherapy (table 1 and table 2).

Neutropenia is often categorized as mild, moderate or severe, based upon the level of ANC. Mild neutropenia corresponds to an absolute neutrophil count between 1000 and 1500/microL, moderate between 500 and 1000/microL, and severe with less than
500/microL. The risk of infection begins to increase at an ANC below 1000/microL (table 2).

Leukopenia and granulocytopenia are generally used interchangeably with neutropenia, although they are somewhat different:

- Leukopenia refers to a low total white blood cell count that may be due to any cause (eg, lymphopenia and/or neutropenia); however, almost all leukopenic patients are neutropenic since the number of neutrophils is so much larger than the number of lymphocytes
- Granulocytopenia refers to a reduced absolute number of all circulating cells of the granulocyte series (eg, neutrophils, eosinophils, and basophils); however, almost all granulocytopenic patients are neutropenic since the number of neutrophils is so much larger than the number of eosinophils and basophils
- Agranulocytosis literally means the absence of granulocytes, but the term is often incorrectly used to indicate severe neutropenia (ie, ANC less than 500/microL).

INCIDENCE IN NORMAL SUBJECTS

Effect of race and ethnic origin — The above definition of neutropenia (ie, an ANC <1500/microL) is applicable for all ages and ethnic groups except newborn infants who have an elevated ANC for the first few days of life [1,2] and certain populations (eg, African-Americans, Yemenite Jews, Ethiopians, certain Arabs), who normally have slightly lower WBC and ANC [3-6].

Data from the 1999 to 2004 United States NHANES (National Health and Nutritional Examination) Survey indicated a prevalence of neutropenia for the following population groups [6]:

- Black participants — 4.5 percent
- White participants — 0.79 percent
- Mexican-American participants — 0.38 percent

This issue was also studied in a group of 261 healthy women of varying ethnicities recruited in New York City. The incidence of neutropenia (ANC <1500) according to their country of origin was [7]:

- United States Black — 10.5 percent
- Haiti — 8.2 percent
- Barbados/Trinidad-Tobago — 6.4 percent
- Jamaica — 2.7 percent
- Dominican Republic — zero percent
United States or Europe White — zero percent

Neutropenia in African-Americans — There are two reasons for a lower ANC in African-Americans: those with an ANC below 2000/microL have defective granulocyte release from an otherwise normal bone marrow; the majority with ANC above 2000/microL have a compromised bone marrow reserve of PMNs as assessed by measuring the maximum ANC increment after the administration of hydrocortisone [3], or following endurance exercise [8].

In some cases, neutropenia has been traced to a common West African allele, a single nucleotide polymorphisms in the Duffy antigen/receptor chemokine gene (DARC), which acts as a receptor for certain pro-inflammatory cytokines [9,10]. Presence of this Duffy null state protects against malaria and has been shown to provide a survival advantage in leukopenic HIV-infected persons of African ancestry [11]. (See "A primer of red blood cell antigens and antibodies", section on 'Duffy blood group system'.)

Benign familial (ethnic) neutropenia — Those patients with what has been called benign familial neutropenia or benign familial leukopenia do not generate a leukocytosis during infection but are otherwise normal; they generate a fever and tachycardia during infection similar to controls, do not have an increased incidence of infection, and do not have an increased risk for febrile neutropenia secondary to myelosuppressive therapy [4,5,12].

Given that benign familial neutropenia has been reported in several ethnic groups, including Yemenite Jews, Blacks of South African extraction, West Indians, and Arab Jordanians, this condition may not be distinct from that described above, and may best be termed "benign ethnic neutropenia" [4,12]. (See "Normal neutrophil development and kinetics".)

ETIOLOGY OF ISOLATED NEUTROPENIA — The causes of isolated neutropenia can be classified by mechanism or by etiologic agent. Neutropenia results from four basic mechanisms: decreased production, ineffective granulopoiesis, shift of circulating PMNs to vascular endothelium or tissue pools, or enhanced peripheral destruction. Confirmation of one of these mechanisms requires leukokinetic studies employing bone marrow cultures, radionuclide tagging of blood PMNs, and other monitoring devices not readily available outside the research laboratory. (See "Normal neutrophil development and kinetics".)

Thus, classification based on whether the neutropenia is acquired or congenital and grouped by known causes or associations provides a more practical means to approach the differential diagnosis of these clinical conditions (table 3).

Acquired neutropenias — There are many acquired causes of neutropenia, with infection, drugs, and immune disorders being the most common.
Postinfectious neutropenia — Infectious neutropenias may represent the most common cause of acquired isolated neutropenia. A number of bacterial, viral, parasitic and rickettsial infections are responsible. In most instances, particularly with viral infections, the neutropenia is short-lived and rarely results in bacterial superinfection. Mechanisms include redistribution, sequestration and aggregation, and destruction by circulating antibodies. Hepatitis B virus, Epstein-Barr virus and human immunodeficiency virus can be associated with more severe and protracted neutropenia. (See "Neutropenia associated with infections").

Drug-induced neutropenia and agranulocytosis — Drug induced neutropenia occurs as an adverse idiosyncratic reaction and is the second most common cause of neutropenia. The true incidence of drug-induced neutropenia is not known; the reported incidence of the rare, more severe, agranulocytosis ranges from approximately 1 to 10 cases per million population per year. The usual definition excludes known cytotoxic agents and requires that the drug have been administered within four weeks of the onset of neutropenia. The drugs with the highest risk of inducing severe neutropenia include clozapine, the thionamides (antithyroid drugs), and sulfasalazine (table 4). These drugs appear to cause neutropenia either by immune-mediated destruction of circulating neutrophils by drug-dependent or drug-induced antibodies or by direct toxic effects upon marrow granulocytic precursors. (See "Drug-induced neutropenia and agranulocytosis").

Primary immune disorders — Antineutrophil antibodies mediate neutrophil destruction either by splenic sequestration of opsonized cells or by complement-mediated neutrophil lysis. Immune neutropenia can occur as a myeloid specific syndrome or in association with other cytopenias. Antineutrophil antibodies are involved in the pathophysiology of the neutropenia caused by some infections, drug exposure, and immune deficiencies. In addition, there are specific primary immune disorders characterized by neutropenia and antineutrophil antibody production. These disorders are discussed in detail elsewhere and will only be summarized here. (See "Primary immune neutropenia").

- Transfusion reactions — Neutrophils share surface antigens with other tissues including HLA antigens and also have specific antigens which can cause transfusion reactions. Recipients of repeated granulocyte transfusions often become alloimmunized.
- Isoimmune neonatal neutropenia — Moderate to severe neutropenia can occur in newborn infants secondary to transplacental passage of IgG antibodies directed against neutrophil specific antigens inherited from the father of the infant. The pathogenesis of this disorder is identical to that of Rh hemolytic disease. The neutropenia is usually noted in an otherwise normal infant and these patients typically do well. In the unusual case with marrow arrest and infection, granulocyte transfusions or granulocyte colony-stimulating factor (G-CSF) are of value.
• Chronic autoimmune neutropenia — Autoimmune neutropenia occurs primarily in infants and children under age 4 and is also called chronic benign neutropenia of infancy and childhood. Most patients present with recurrent infections. Specific treatment of neutropenia is usually not required. Many patients remain free of infections and maintain a normal lifestyle with no or minimal medical intervention. Spontaneous remission with disappearance of autoantibodies is common.

• Chronic idiopathic neutropenia — The term chronic idiopathic neutropenia, also known as benign chronic neutropenia, is used to describe chronic neutropenia for which there is no obvious cause. In contrast to autoimmune neutropenia, which is primarily a disease of infants and young children, chronic idiopathic neutropenia tends to occur in late childhood or adulthood and does not undergo spontaneous remission. Serologic abnormalities and evidence of antibody production have been found in 30 to 40 percent. These patients most often have a benign course despite the degree of neutropenia. The presence of some marrow reserve may explain the frequent lack of excess infections. (See "Primary immune neutropenia", section on 'Chronic idiopathic neutropenia'.)

• Pure white cell aplasia — Pure white cell aplasia is a rare disorder characterized by complete disappearance of granulocytopenic tissue from the bone marrow. It is often associated with thymoma and is due to the presence of antibody mediated GM-CFU inhibitory activity. (See "Primary immune neutropenia", section on 'Pure white cell aplasia'.)

• Other autoimmune disorders — Other immune disorders which are associated with neutropenia include T-gamma lymphocytosis (large granular lymphocyte syndrome) and Felty's syndrome. In the former disorder, there is infiltration of the bone marrow with large granular lymphocytes (LGL), most often due to a clonal expansion of cytotoxic T-cells and often associated with rheumatoid arthritis. (See "Large granular lymphocyte syndrome in rheumatoid arthritis" and "T cell large granular lymphocyte leukemia".)

Antibodies to granulocyte colony-stimulating factor (C-CSF) may play a role in the neutropenia of Felty's syndrome. One small observational study found elevated levels of antibodies to human G-CSF in the serum of a majority of patients with Felty's syndrome (11 of 15) but not in non-neutropenic patients with rheumatoid arthritis (0 of 16) [13]. (See "Clinical manifestations and diagnosis of Felty's syndrome".)

Antineutrophil antibodies and occasional mild neutropenia can also be seen in hyperthyroidism, Wegener's granulomatosis, rheumatoid arthritis, and systemic lupus erythematosus. (See "Hematologic manifestations of systemic lupus erythematosus in adults".)

• Complement activation — The exposure of blood to artificial membranes as in dialysis and extracorporeal membrane oxygenation may result in complement
activation in vivo. The complement is typically produced by the classic complement activation pathway and induces neutrophil aggregation and adherence to endothelial surfaces, often in the lung. Neutropenia and cardiopulmonary symptoms typically occur shortly after exposure to the membrane. This complication can be prevented during hemodialysis by using biocompatible membranes. (See "Reactions to the hemodialysis membrane".)

Hypersplenism — Enlargement of the spleen from any etiology can result in neutropenia, due to splenic trapping [14]. The severity of neutropenia is related to the size of the spleen and rarely is sufficient to result in severe infection. (See "Extrinsic nonimmune hemolytic anemia due to mechanical damage: Fragmentation hemolysis and hypersplenism").

Bone marrow disorders — A number of diseases affecting the bone marrow are associated with neutropenia (table 3). In most cases, such as aplastic anemia, the leukemias, myelodysplasia, and postchemotherapy, the neutropenia is not an isolated defect, and is associated with varying degrees of anemia and thrombocytopenia. Examination of the peripheral smear and a bone marrow aspirate with biopsy are helpful in making these diagnoses.

Congenital neutropenias — Rare primary neutropenias occur and, when associated with severe recurrent infections as in the severe congenital neutropenias, can be treated successfully with hematopoietic growth factors. These syndromes include severe infantile agranulocytosis, myelokathexis, Shwachman-Diamond-Öski syndrome, Chediak-Higashi syndrome, and reticular dysgenesis. The diagnosis is made by examination of the bone marrow which reveals myeloid hypoplasia. Congenital neutropenia can also be seen with certain inborn errors of metabolism such as glycogen storage disease and with some of the primary immune deficiency states. (See "Congenital neutropenia" and "Shwachman-Diamond syndrome").

Cyclic neutropenia is characterized by recurrent mouth infections and regular oscillations in the numbers of blood neutrophils, monocytes, eosinophils, lymphocytes and reticulocytes at approximately 21 day intervals. It usually presents in childhood, as a familial syndrome, but there is a subset of patients with onset in adulthood. Treatment is largely supportive and G-CSF has been effective in the unusual case with severe recurrent infections. (See "Cyclic neutropenia").

Myeloperoxidase deficiency — In many clinical laboratories, neutrophils are identified on the white blood cell differential by virtue of their positivity for myeloperoxidase. Patients with myeloperoxidase deficiency may then be erroneously considered as having severe neutropenia. This subject is discussed separately. (See "Myeloperoxidase deficiency and other enzymatic WBC defects causing immunodeficiency", section on 'Myeloperoxidase deficiency'.)
deficiency' and "Automated hematology instrumentation", section on Siemens Advia (and H series).)

CLINICAL PRESENTATION — Recurrent infections are the only significant consequence of neutropenia. However, the classic signs of infection are often less evident in patients with neutropenia. This is particularly true in patients with bone marrow hypoplasia who are unable to respond to infection. In this setting, radiographs may not demonstrate pneumonia, or the patient may not exhibit abnormal tenderness with an early ruptured viscus.

The propensity to infection in neutropenic patients is primarily related to the ANC level and the duration of neutropenia (table 2). Common sites of infection include the oral cavity and mucous membranes, the skin, and, with severe, persistent neutropenia, systemic infections of the lungs and bloodstream may occur. Endogenous bacterial flora are the most common pathogens.

Risk of infection — In a classic study in patients with leukemia published in 1966, the relationship between the frequency of infection and both the severity and duration of neutropenia was evaluated during 733 episodes of moderate neutropenia (ANC less than 1000/microL) and 125 episodes of severe neutropenia (ANC less than 100/microL) [15]. Identified infections occurred in 80 percent of patients with severe neutropenia within two weeks of onset and in 100 percent at three weeks.

Although the absolute risk of infection is lower in more recent studies, the relationship between the degree of neutropenia and infectious risk still applies. It holds particularly well in situations in which neutrophil production is affected at the stem cell or myeloblast stage of maturation and/or the marrow is hypocellular. In comparison, the degree of neutropenia does not correlate as well with a propensity to infection in neutropenic patients who have an adequate bone marrow reserve of band forms and PMN.

These relationships can be illustrated by the following observations:

- Patients with an ANC <500/microL due to chemotherapy, marrow failure, or marrow exhaustion are at high risk for overwhelming bacterial infection [15-17]. This is particularly true in cancer patients with an ANC <100/microL for more than five days [18]. The source of microbial invasion of the blood is chemotherapy-induced mucositis and breaks in the gastrointestinal lining.
- Efforts have been made to identify febrile neutropenic patients with a lower risk of bacteremia. In one pediatric study of 161 patients experiencing 509 episodes of fever and neutropenia, presentation with chills or hypotension, the requirement for fluid resuscitation, or the diagnosis of leukemia or lymphoma were associated with a higher probability of positive blood cultures [19]. Children without initial signs of
sepsis, whose fever resolved on antibiotic therapy, and whose ANC was 100/microL or higher after a 48 hour period in hospital had a low risk of complications.

- The risk is lower in patients with AIDS who may develop neutropenia in whom drug toxicity or autoimmunity may be responsible for the neutropenia. The risk for bacterial infection becomes significant when the ANC is less than 750 to 1000/microL [20,21]. In one series of 2047 HIV-infected patients, the risk for developing a bacterial infection requiring hospitalization occurred at ANCs below 750/microL and increased progressively as the ANC fell below this level (figure 1) [20]. (See "Neutropenia associated with infections", section on 'Human immunodeficiency virus'.)

- Children with the benign chronic neutropenia may have an ANC below 200/microL for months or years and remain free of serious infections [22]. Similarly, some adults with immune neutropenia have severe depression of the ANC but never suffer episodes of infection [23]. In both situations, the bone marrow generally shows normal granulocyte maturation up to either the metamyelocyte or band form stage with a paucity of PMNs. This bone marrow picture is referred to as a "maturational arrest".

- Well-appearing children with transient neutropenia, particularly of short duration, are also at low risk for infection. In one study of 119 children, infectious complications occurred in 4 of the 36 patients who had neutropenia for more than 30 days (two with stomatitis, one with cellulitis, and one with pneumonia) but in none with a shorter duration of neutropenia [24].

In addition to differences in bone marrow reserve, several other factors may contribute to the variability in infectious risk. Many patients with chronic forms of neutropenia have normal or increased blood monocyte counts. Monocytes are functioning phagocytes like the neutrophil and band forms and probably contribute to the lack of correlation between the ANC and infection risk [25,26].

Another difference is that the delivery of neutrophils to tissues in chronic severe neutropenia appears to be greater than in acute chemotherapy-induced neutropenia of equal degree [18,27]. Furthermore, recovery of neutrophils is evident at tissue sites before the blood [27]. These observations indicate that the ANC does not always accurately reflect neutrophil availability at tissue or organ sites of infection.

Specific pathogens associated with neutropenia — The specific pathogens isolated from infected neutropenic patients are almost exclusively pyogenic or enteric bacteria or certain fungi. They are usually endogenous bacteria including Staphylococcus aureus from the skin and Gram negative organisms from the gastrointestinal and urinary tract. Isolated neutropenia does not increase the susceptibility to viral or parasitic infection.
Common sites of infection include the oral cavity and mucous membranes, the skin, and perirectal and genital areas. With persistent severe neutropenia, systemic infection occurs associated with bacteremia, and infections of the lung and gastrointestinal tract. Patients receiving broad spectrum antibiotics for two weeks or more while neutropenic are more prone to infection with enteric bacteria and/or fungi, while patients with indwelling catheters or other foreign bodies are more likely to become infected with coagulase-negative staphylococci.

One study evaluated the distribution of organisms for 909 episodes of bacteremia and associated outcome among 799 neutropenic febrile cancer patients (table 5A-B) [18]. Among the bacteremic episodes, 46 percent were due to Gram positive organisms, 42 percent to Gram negative organisms, and 12 percent were polymicrobial. Infection at a site other than blood alone was observed in 242 episodes; the sites of involvement include lung (about 40 percent), skin and soft tissue (about 30 percent), urinary tract, sinuses and oropharynx, skeletal, enteric tract, meninges, and endocardium [18]. In general, the initial and ultimate response rates were good when the infection was due to a single type of organism and less favorable when the infection was due to more than one type of microbe.

DIAGNOSTIC APPROACH — The first step in the approach to the patient with neutropenia is confirmation of the diagnosis. Review of a Wright—Giemsa stained peripheral blood smear will confirm the reduced number of neutrophils. In all cases in which the white blood cell differential count has been generated by automatic counters, it should be repeated manually. Pseudoneutropenia can occur if blood is left standing for a prolonged period of time and in the presence of paraproteinemia and certain anticoagulants which can cause clumping.

Infants and young children — The differential diagnosis of neutropenia in infants and young children includes isoimmune neonatal neutropenia, severe congenital neutropenia (SCN), Shwachman Diamond-Oski syndrome, autoimmune neutropenia, and cyclic neutropenia.

- Isoimmune neutropenia presents as moderate to severe neutropenia with or without associated sepsis in newborn infants. The diagnosis is made by detection of antineutrophil antibodies in infant and maternal serum. (See "Primary immune neutropenia".)
- Severe congenital neutropenia (SCN) is characterized by severe infections in the first month of life, the absence of spontaneous remissions, and maturation arrest of myelopoiesis at the promyelocyte stage. (See "Congenital neutropenia".)
- Shwachman Diamond-Oski syndrome is characterized by pancreatic insufficiency, metaphyseal dysostosis, neutropenia with or without thrombocytopenia, and/or anemia. (See "Congenital neutropenia".)
Autoimmune neutropenia is usually not associated with recurrent severe infections and typically occurs later (between the ages 5 to 15 months but the range extends from one month to adulthood) than the first two conditions. Although unusual, a small number of patients with autoimmune neutropenia can present with features characteristic of SCN and the differential diagnosis is ultimately made by detection of granulocyte-specific antibodies in the patients' sera. (See "Primary immune neutropenia").

Cyclic neutropenia classically occurs as neutropenic periods of three to six days approximately every 21 days. The diagnosis is made by monitoring the ANC three times per week for six to eight weeks. (See "Cyclic neutropenia").

Children or adults — If anemia, particularly normocytic or macrocytic anemia, or thrombocytopenia is found in the child or adult with neutropenia, examination of the peripheral smear along with a bone marrow aspiration should be performed immediately unless the cause is clear (eg, chemotherapy). In other cases, the intensity of the diagnostic approach is dependent upon the severity of the clinical presentation.

Mild neutropenia in the absence of recurrent or protracted infection — Most causes of mild neutropenia are benign. Thus, a period of observation is indicated if the patient is asymptomatic, particularly if there is a recent history of viral infection or a medication has been taken which is known to be associated with neutropenia (table 3). Examination of the oral cavity is important since the presence of gingivitis or tooth abscess suggests the presence of symptomatic neutropenia.

During the period of observation, the ANC should be measured three times per week for six to eight weeks to rule out cyclic neutropenia. If available, testing for antineutrophil antibodies may provide useful information.

If the neutropenia resolves, the patient should be followed for one year with complete blood count being obtained whenever fever occurs. If the neutropenia persists after an eight week observation period, a bone marrow examination is indicated, and the sequence described for patients with recurrent infection should be followed.

Moderate to severe neutropenia with recurrent infection — Bone marrow aspiration with evaluation of cellularity and morphology should permit identification of late myeloid arrest or myeloid hypoplasia. Late arrest is seen in idiopathic or autoimmune neutropenia, most often associated with antineutrophil antibodies, and in collagen vascular diseases, some drug-induced neutropenias, and chronic infection. Myeloid hypoplasia characterizes toxic drug-induced neutropenias, pure white cell aplasia, T-gamma lymphocytosis (large granular lymphocyte syndrome), severe congenital neutropenia, and myelodysplastic syndrome.
Patients who have episodic infections should have twice weekly measurement of the ANC for at least six weeks to confirm the diagnosis of cyclic neutropenia. Patients with cyclic neutropenia have decreased marrow cellularity a week before the nadir of their neutropenia. (See "Cyclic neutropenia".)

If the diagnosis is not apparent after examination of the bone marrow aspirate, further laboratory studies are indicated:

- Antinuclear antibodies and complement to screen for collagen vascular disease
- Antineutrophil antibodies to screen for immune neutropenia (see "Laboratory evaluation of neutropenia and neutrophil dysfunction")
- Immunoglobulins and immune evaluation to screen for defects of cellular or humoral immunity (see "Laboratory evaluation of the immune system")
- Screen for HIV infection (see "Diagnostic assays for HIV infection")
- Serum vitamin B12 and folate concentrations to screen for deficiency of these vitamins (see "Diagnosis and treatment of vitamin B12 and folic acid deficiency")
- Bone marrow culture to evaluate CFU-GM production in pure white cell aplasia (see "Primary immune neutropenia")

GENERAL ASPECTS OF TREATMENT — The clinical management of neutropenic states depends upon the cause and degree of the neutropenia and any associated disease states. Patients with severe neutropenia and little marrow reserve may have sepsis, while patients with hypercellular marrow tend to have chronic infections or no infection. (See "Approach to the immunocompromised patient with fever and pulmonary infiltrates" and "Fever in the neutropenic adult patient with cancer".)

All patients with chronic neutropenia should receive regular dental care. Chronic gingivitis and recurrent stomatitis can be major sources of morbidity. Antibiotic mouthwashes, such as Peridex, can be used to decrease gingivitis. Prophylactic antibiotics are of no value.

Patients with bone marrow hypoplasia and/or severe infections — This group includes patients with chemotherapy-induced neutropenia or bone marrow granulocyte hypoplasia. There are multiple causes of the latter problem such as aplastic anemia, severe congenital neutropenia, Shwachman Diamond-Oski syndrome, pure white cell aplasia, large granulocyte lymphocyte syndrome, and drug-induced (toxic-form) agranulocytosis. The general approach involves preventive measures to limit the number and severity of infections and aggressive treatment of infections that occur. Patients should also receive aggressive antibacterial therapy for fever, even in the absence of signs of infection.

G-CSF should be given to patients with an inadequate response to antibiotics or recurrent severe infections and to all infants with severe congenital neutropenia.
Antibiotic therapy — The organisms that cause infections in patients with severe neutropenia usually come from the gastrointestinal tract or skin and can result in the rapid onset of overwhelming sepsis. Thus, febrile patients with neutropenia related to marrow suppression should be treated immediately, following culture of body fluids, with broad-spectrum parenteral antibiotics for coverage of both Gram positive and Gram negative bacteria [28].

In general, patients with an ANC greater than 1000/microL can be managed on an outpatient basis while those with an ANC of less than 500/microL and marrow aplasia should always be treated on an inpatient basis with parenteral antibiotics (table 2). Routine reverse isolation procedures are of no benefit and serve to decrease contact with medical personnel [29,30].

Antibiotics should be continued for several days after the fever has subsided unless the ANC has risen above 500/microL in which case the antibiotics can be discontinued as long as no source of infection is apparent [28]. If fever persists, other therapies should be considered.

- If fever and neutropenia persist beyond seven days in the immunosuppressed patient, *amphotericin B* should be started empirically [28].
- Granulocyte transfusions should be given, if available, to patients with Gram negative sepsis who have not shown a clinical response to antibiotics within 24 to 48 hours. Enthusiasm for the use of granulocyte transfusions has waned due in part to difficulties in procurement, to better antibiotics, and to the use of bone marrow growth factors. However, better methods of procurement and their rapid efficacy makes them a useful part of the armamentarium for treating neutropenic patients with sepsis. (See "Granulocyte transfusions".)
- Corticosteroid therapy has been effective in some instances of immune-mediate neutropenia, as has high-dose intravenous immune globulin (1 to 2 g/kg for one to two days) [26,31]. (See "Primary immune neutropenia".)

Myeloid growth factors — The administration of recombinant *granulocyte colony-stimulating factor* (G-CSF, filgrastim) can correct the neutropenia and reduce infectious morbidity in infected patients with a variety of causes of severe neutropenia. Included in this group are severe congenital neutropenia, cyclic neutropenia, and AIDS [32-39]. GM-CSF has also been used successfully in neutropenic patients with AIDS [38] but appears to be less effective than G-CSF in patients with cyclic neutropenia [36]. (See "Fever in the neutropenic adult patient with cancer".)

The potential efficacy of the appropriate use of G-CSF can be illustrated by the following observations:
A multicenter, phase III trial randomized 123 patients with severe chronic neutropenia and recurrent infection to either immediate treatment with filgrastim (3.45 to 11.5 microg/kg per day) or a four month observation period followed by filgrastim treatment [33]. On treatment, 108 patients had a median ANC greater than or equal to 1500/microL and bone marrow aspirates showed increased proportions of maturing neutrophils. Filgrastim therapy was associated with a reduction in the incidence and duration of infection-related events of approximately 50 percent.

Another 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 [37]. 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.

However, G-CSF therapy is not indicated for all causes of neutropenia. It is helpful in patients with neutropenia associated with early myeloid arrest and its use should be reserved for patients with demonstrated infectious morbidity related to the neutropenia.

Chemotherapy-induced neutropenia — This subject is discussed in depth separately. (See "Prophylaxis of infection during chemotherapy-induced neutropenia" and "Fever in the neutropenic adult patient with cancer".)

Hematopoietic cell transplantation — Hematopoietic cell transplantation has been used successfully in certain instances of severe neutropenia, such as infantile agranulocytosis [40]. It should be considered if an appropriate donor is available and no therapeutic response is achieved with G-CSF or GM-CSF. (See "Congenital neutropenia", section on 'Infantile agranulocytosis'.)

Patients with adequate marrow reserves — Patients with late marrow arrests and a normocellular marrow have an adequate bone marrow supply of neutrophils and usually handle infections reasonably well. Children in whom the diagnosis of chronic benign neutropenia of infancy has been confirmed can be treated like normal children. Less aggressive therapy is also warranted in adults with an adequate bone marrow reserve and a several month history of severe neutropenia without serious infection. However, the subsequent course is not known when these patients are first encountered. As a result, they should initially be treated like other patients with severe forms of neutropenia.

Long-term follow-up of patients with severe combined neutropenia and Shwachman-Diamond-Oski syndrome receiving G-CSF has indicated a 9 percent incidence of acute myeloid leukemia or myelodysplasia. It is unclear whether G-CSF is a risk factor since
patients with both disorders have developed AML/MDS prior to the use of G-CSF [41].
(See "Congenital neutropenia").
INTRODUCTION — Fever in a neutropenic patient should be considered a medical emergency. Prior to the era of empiric antibiotic therapy, infections accounted for almost 75 percent of the mortality related to chemotherapy. With the availability of broad-spectrum antibiotics, more aggressive chemotherapeutic regimens have been used. Although initially designed for patients undergoing chemotherapy for leukemia or lymphoma, empiric antibiotics are now initiated in all febrile patients with chemotherapy or drug-induced neutropenia [1-6].

The predisposing factors, pathogenesis, diagnosis, and treatment of patients with febrile neutropenia will be reviewed here. The approach to immunocompromised patients with fever and rash or fever and pulmonary infiltrates are discussed separately. (See "Fever and rash in non-HIV immunocompromised hosts" and "Approach to the immunocompromised patient with fever and pulmonary infiltrates".)

DEFINITIONS — Fever in a neutropenic patient is usually defined as a single temperature of >38.3°C (101°F), or a sustained temperature >38°C (100.4°F) for more than one hour [1]. However, on occasion a neutropenic patient may not present with fever despite the presence of infection. This can occur more commonly in elderly patients or those receiving corticosteroids. The clinician should recognize that neutropenic patients may present with hypothermia, hypotension, or clinical deterioration as the initial signs of occult infection. Consequently there should be a low threshold for starting empiric antibiotics, especially if there are signs of clinical deterioration, even in the absence of fever.

The definition of neutropenia varies from institution to institution but is usually defined as an absolute neutrophil count (ANC) <500 cells/microL or <1000 cells/microL with a predicted nadir of <500 cells/microL [1]. The ANC can be calculated by multiplying the total white blood cell count by the percentage of neutrophils and bands.

PREDISPOSING FACTORS — The risk of infection in the neutropenic patient is related to the virulence of the pathogen, the immunologic impairment of the host, and the disruption of skin and mucosal barriers [7]. (See 'Associated pathogens' below and 'Pathogenesis' below.)
The incidence of an occult infection in a febrile neutropenic patient increases with the severity of the neutropenia. While the risk of an occult infection increases with an ANC <1000 cells/microliter, it is substantially higher for those with an ANC <500 cells/microliter and is highest for those with an ANC <100 cells/microliter. Morbidity and mortality is also increased in patients with profound neutropenia (ANC <100/microliter) [2-6]. In addition to the degree of neutropenia, other risk factors for occult infection have been identified including:

- A rapid decline in ANC
- Prolonged duration of neutropenia (>7 to 10 days)
- Cancer not in remission [8]
- Comorbid illnesses requiring hospitalization [8,9]
- Use of peripheral lines and central venous catheters [10-12]
- Use of monoclonal antibodies against various cellular receptors [13].

PATHOGENESIS — Contributory factors to the pathogenesis of febrile neutropenia include the direct effects of chemotherapy on mucosal barriers and immune deficits related to the underlying malignancy [12].

Chemotherapy-induced mucositis occurs throughout the alimentary system, and seeding of the bloodstream from endogenous flora in the GI tract is believed to explain a majority of febrile neutropenic episodes. Obstruction of the lymphatics, biliary tract, bronchial, gastrointestinal or urinary systems by tumors or as a result of surgical procedures is also a common cause of infections.

Immune defects related to underlying hematologic disorders, in addition to the immunosuppressive effects of chemotherapy also place patients at higher risk for infections. In one study, patients who developed severe infection or died had a significant decrease in phagocytic activity of neutrophils compared to those with only a mild infection, suggesting that neutrophils might be preactivated and have reduced function prior to the initiation of chemotherapy [14]. Furthermore, the administration of chemotherapy not only decreases the number of neutrophils, but also results in chemotactic and phagocytic defects as well.

The risk for specific types of infections is influenced by the nature of the underlying malignancy and its associated humoral or cellular immune deficits:

- Abnormal antibody production or clearing of immune complexes in multiple myeloma, chronic lymphocytic leukemia (CLL) and splenectomized (including functional asplenia) patients, results in an increased risk of sepsis from encapsulated organisms, including Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, and Capnocytophaga canimorsus. (See "Clinical features"
and management of sepsis in the asplenic patient", section on 'Risk of other infections'.

- The T cell defects associated with Hodgkin lymphoma result in an increased risk of infection with intracellular pathogens such as Listeria monocytogenes, Salmonella, Cryptococcus neoformans, and Mycobacterium tuberculosis. Patients with acute lymphocytic leukemia (ALL), central nervous system (CNS) tumors, and other cancer patients receiving high dose steroids are at increased risk of Pneumocystis jiroveci (previously P. carinii) pneumonia (PCP). (See appropriate individual topics).

ASSOCIATED PATHOGENS — An infectious source is identified in approximately 30 percent of febrile neutropenic episodes [5]. Often the only evidence of infection is bacteremia, which can be documented in approximately 25 percent of patients. Approximately 80 percent of identified infections are believed to arise from patients' own endogenous flora [15]. Table 1 lists the range of pathogens found in these patients (table 1).

Bacterial pathogens — Gram-negative bacilli, particularly P. aeruginosa, were the most commonly identified pathogens until the 1980s [16]. In a survey of 49 hospitals in the United Status in 1995 and 2000, gram-positive organisms accounted for 62 and 76 percent of all bloodstream infections, whereas gram-negative organisms accounted for only 22 and 14 percent of all bloodstream infections [17]. Common gram-positive cocci include Staphylococcus aureus, Staphylococcus epidermidis, and streptococci; less common gram-positive organisms include Corynebacterium jeikeium, Bacillus, Leuconostoc, Lactobacillus, Propionibacterium acnes, and Rhodococcus species [18].

A number of factors may account for the trend toward gram-positive infections, including the introduction of long-term indwelling lines (Hickman-Broviac, Portacaths, etc), the empiric antibiotic regimens that were designed to cover P. aeruginosa, the use of prophylactic antimicrobials that are primarily active against gram-negative pathogens (eg, fluoroquinolones), and newer chemotherapeutic regimens.

However, it remains important to cover broadly for gram-negative pathogens because of their virulence and association with sepsis [19,20]. Furthermore, gram-negative organisms continue to cause the majority of infections in sites outside of the bloodstream (eg, respiratory, biliary, urinary, and skin) [7]. In addition, a rising number of infections are polymicrobial [19,20]. Clinicians also need to be aware of the microbiology surveillance data from their own institution, which can vary dramatically from center to center [19,21].

Although anaerobic bacteria are present in abundance in the alimentary tract, it is usually not necessary to add specific anaerobic antibiotic coverage to the initial empiric regimen. Anaerobic bacteremia occurred in 3.4 percent of episodes in a large series of cancer patients from France [22] and anaerobic bacteria are often part of polymicrobial infection
Specific anaerobic coverage should be added if there is evidence of necrotizing mucositis, sinusitis, periodontal abscess, perirectal abscess/cellulitis, intraabdominal or pelvic infection, typhlitis (necrotizing neutropenic colitis), or anaerobic bacteremia. (See "Necrotizing enterocolitis (typhlitis) in adults" and "Enterotoxicity of chemotherapeutic agents").

Fungal pathogens — Fungal pathogens are common. The risk for invasive fungal infections increases with the duration and severity of neutropenia, prolonged antibiotic use, and number of chemotherapy cycles. However, fungal infections can also present early or even prior to initial chemotherapy [25]. In an autopsy study of patients who died after prolonged febrile neutropenia between 1966 and 1975, 69 percent of patients had evidence of systemic fungal disease [26].

The following observations have been made about specific fungal pathogens:

- Candida albicans and other yeasts are common fungal causes of line infections and can cause disseminated candidiasis. Among patients who develop disseminated candidiasis following chemotherapy, hepatosplenic involvement is common; symptoms are often not present until the neutropenia resolve. (See "Hepatosplenic candidiasis (chronic disseminated candidiasis)".)
- Aspergillus is a common fungal pathogen in immunocompromised hosts; manifestations vary from localized skin ulcers, sinusitis and invasive pneumonia, to fulminant disseminated disease [27]. (See "Clinical features and diagnosis of invasive aspergillosis").
- Fusarium spp have also been increasingly reported in the immunocompromised host [28-31]. (See "Fusarium infection").
- Reactivation of endemic fungi (histoplasmosis, blastomycosis, and coccidioidomycosis) or tuberculosis should also be considered in appropriate patients with prolonged steroid use or other immune suppression. (See appropriate individual topics).

Viral pathogens — Viral infections, especially human herpes viruses, are also common in this patient population.

Herpes simplex viruses, HSV-1 and HSV-2, are common causes of skin eruptions. HSV can cause a wide variety of clinical syndromes, including encephalitis, meningitis, myelitis, esophagitis, pneumonia, hepatitis, erythema multiforme, and ocular disease. Herpes zoster often presents in an atypical disseminated pattern involving multiple dermatomes or widespread skin dissemination in immunocompromised hosts. Immunocompromised patients with disseminated varicella zoster virus (VZV) infection can have pulmonary involvement and should be placed on respiratory precautions to prevent aerosolized transmission to susceptible individuals.
Primary seroconversion or reactivation of other human herpes viruses (cytomegalovirus, Epstein Barr virus, HHV-6) can also occur in this patient population as a result of immunosuppression and transfusions. Other common treatable viral infections that occur in the neutropenic host include respiratory syncytial and influenza viruses.

Other — Reactivation of tuberculosis should be considered in appropriate patients with prolonged steroid use or other forms of immunosuppression. Babesia microti or B. divergens infection can also cause overwhelming sepsis in the patient with compromised splenic function. (See "Epidemiology and pathogenesis of babesiosis".)

PATIENT EVALUATION — All febrile neutropenic patients should have a careful history and detailed physical examination.

Physical examination — A thorough general physical examination should be performed including the sinuses, fundi, and perirectal area. It is always important to remember that in the absence of neutrophils, signs of inflammation can be extremely subtle.

The skin and mucous membranes should be examined for signs of erythema, rash, cellulitis, ulcers, furuncles, herpetic eruptions, paronychia, mucositis, dental or peritonsillar abscesses, or pilonidal disease. Skin lesions can often be a manifestation of a systemic infection including:

- Ulcers — fungi, atypical bacteria, mycobacteria, viruses
- Ecthyma gangrenosum — large lesion with a necrotic center that is classically seen with P. aeruginosa but also other bacteria such as S. aureus (picture 1)

Sometimes skin lesions such as erythema multiforme can be related to viral infections; alternatively E. multiforme can be related to antibiotic therapy and may be associated with fever, causing diagnostic confusion (picture 2). (See "Drug eruptions".)

The examination should also include inspection of the perianal area. A digital rectal examination (and rectal temperatures) generally should be avoided. However, if a perirectal abscess or prostatitis is suspected, a gentle rectal examination can be performed after broad-spectrum antibiotics have been administered.

All indwelling or recent line sites should be carefully examined for subtle signs of infection; slight erythema, tenderness, fluctuance, or an exudate may be the only evidence of a serious "tunnel" infection. Lines should also be assessed for any malfunction; difficulty with infusion or blood drawing can also be a sign of an infected clot even in the absence of a problem with the exit site.
Review of symptoms and a physical examination should be repeated daily. In one prospective assessment of 968 episodes of fever and neutropenia in patients who did not respond to initial treatment, 41 percent of patients still had unexplained fevers at 72 hours and new sites of infection (eg, lungs, skin, and urinary tract) became apparent in another 11 percent [32]. In addition, as the ANC rebounds, symptoms and signs of an infection often become evident.

Laboratory studies — Laboratory evaluations should include a complete blood cell count with differential, transaminases, bilirubin, amylase, electrolytes, and cultures. Lumbar puncture is not necessary routinely but should be performed in patients who have a change in mental status.

Checking fungal markers from the serum, such as galactomannan antigen and beta-D-glucan, should also be considered. Galactomannan antigen is a specific test for invasive aspergillosis, whereas beta-D-glucan is a nonspecific test for several invasive fungal infections including aspergillosis and candidiasis. (See "Clinical features and diagnosis of invasive aspergillosis", section on 'Galactomannan antigen detection' and "Clinical features and diagnosis of invasive aspergillosis", section on 'Beta-D-glucan assay'.)

In interpreting laboratory results in neutropenic patients, it is important to recognize that the absence of neutrophils cannot be used to exclude the possibility of infection. Therefore, absence of a cerebrospinal fluid pleocytosis, pyuria, or PMNs on sputum Gram stain does not rule out infection.

Microbiology — Specimens for the microbiology laboratory should include two or more blood cultures (some prefer culturing each intravenous port and at least one peripheral blood culture), sputum Gram stain and culture, and urine Gram stain and culture.

Blood cultures should be repeated for persistent fevers or rigors. Institutions may have different guidelines for the frequency of obtaining blood cultures. As an example, we recommend one set of blood cultures a day for patients with a stable fever pattern. Another approach is to draw two or three sets initially and to wait 48 to 72 hours to repeat blood cultures unless the patient has hemodynamic instability, rigors, new localizing symptoms, or another clinical change.

Documenting that an intravenous catheter is the infectious source can be difficult and requires blood cultures taken peripherally and through the central access [11]. This issue is discussed separately. (See "Diagnosis of intravascular catheter-related infections", section on 'Blood cultures'.)

Neutropenic patients with pulmonary infiltrates frequently cannot produce sputum; a more invasive approach including bronchoscopy or open lung biopsy may need to be pursued in
order to make a microbiologic diagnosis. This is may be particularly important for patients with infiltrates on chest radiographs or chest CT who continue to worsen despite 24 to 48 hours of empiric antibiotic therapy.

Imaging — An initial chest x-ray should be obtained on admission, even if the patient does not have pulmonary symptoms.

Chest radiographs should be repeated for increasing or persistent pulmonary symptoms, cough, or shortness of breath. Chest x-ray findings are often minimal or absent even in patients with pneumonia. Radiographic findings may develop ("blossom") along with an increase in symptoms as the neutropenia begins to resolve.

Chest computed tomographic (CT) scanning may demonstrate abnormalities such as pneumonia or pulmonary nodules even when the chest x-ray is normal. As an example, in one study, high-resolution CT demonstrated pneumonia in more than one-half of persistently febrile neutropenic patients who had normal findings on routine chest radiography [33]. It was estimated that high-resolution CT led to a time gain of five days for diagnosis compared to the exclusive use of chest radiography, but did not improve clinical outcomes.

Although CT scanning has not been shown to change clinical outcomes, we have a low threshold for ordering a CT in patients with pulmonary symptoms to help guide the selection and duration of treatment, and to assess for radiographic evidence of invasive fungal disease.

Other — If localizing signs or symptoms are present, other tests should be considered for further investigation, such as imaging of the CNS, sinuses, chest, abdomen, or pelvis, skin biopsy for culture, direct fluorescent antibody (DFA) testing for HSV or VZV, stool for culture, Clostridium difficile toxin, or ova and parasites.

GENERAL TREATMENT PRINCIPLES — Fever in a neutropenic patient should be considered a medical emergency. Broad-spectrum antibiotics should be given as soon as possible and at full doses (adjusted for renal and/or hepatic function). Early studies documented up to a 70 percent mortality if initiation of antibiotics was delayed [34]. The following general principles apply:

- Antibiotics are usually administered empirically, but should always include appropriate coverage for suspected or known infections. However, the antibiotic regimen should still provide broad empiric coverage for the possibility of other pathogens, unlike the treatment strategy in most immunocompetent hosts. (See 'Summary and recommendations' below.)
• Initial antibiotic selection should be guided by the patient's history, allergies, symptoms, signs, recent antibiotic use and culture data, and awareness of institutional nosocomial infection patterns [21].
• Ideally, antibiotics should be bactericidal and should be administered through alternate ports of any indwelling intravenous line.
• Clinical response and culture results should be closely monitored, and therapy should be adjusted in a timely fashion [1-5,35,36].

EMPIRIC THERAPY — The efficacy of the treatment of febrile neutropenia has improved greatly as demonstrated by a progressive decline in mortality rates in clinical trials beginning in 1978 that emphasized prompt initiation of empiric coverage [7]. If the patient continues to have fever after five days without an identifiable source, the following options are available [2]:

• Continue treatment with the initial antibiotic(s) if the patient is clinically stable and the neutropenia is expected to resolve within the ensuing five days.
• Change or add antibiotic(s) if there is evidence of progressive disease or a new complication, such as the onset of abdominal pain due to enterocolitis (typhlitis), new or worsening mucous membrane lesions, pulmonary infiltrates, or drug toxicity.
• Add an antifungal drug to the regimen, with or without changing the antibiotics, if the neutropenia is expected to persist for more than five to seven days. (See 'Addition of antifungal drugs' below.)

Antibiotic selection — The choice of antibiotics is driven by multiple factors, including whether an agent is bactericidal or not [19]. Some antibiotics, such as aminoglycosides and fluoroquinolones, exhibit concentration-dependent killing and are important in the treatment of gram-negative sepsis. Other drugs, such as beta-lactams, exhibit time-dependent killing. When using beta-lactams, correct dosing intervals should be used to assure that drug concentrations are greater than the minimal inhibitory concentration for the pathogen.

Initial empiric antibiotic guidelines adapted from the IDSA executive summary appear in the Table (table 2A-B) [1]. Initial therapy can include use of one or two drugs; the selected choice is usually a matter of clinical practice and experience at each hospital [21].

The IDSA clinical practice guidelines for the use of antimicrobial agents in neutropenic patients with cancer, as well as other IDSA guidelines, can be accessed through the Infectious Diseases Society of America's web site [37].

Combination therapy — Numerous antibiotic regimens have been studied as initial empiric therapy in febrile neutropenia, and none have been shown to be clearly superior [38,39].
One approach is to use an extended spectrum beta-lactam (e.g., piperacillin, ceftazidime) in combination with an aminoglycoside. Other examples of combination regimens include double beta-lactams or a beta-lactam and a fluoroquinolone.

- A meta-analysis of eight randomized controlled trials that compared ciprofloxacin/beta-lactam combinations to aminoglycoside/beta-lactam regimens for the treatment of febrile neutropenia demonstrated similar overall efficacy for clinical cure and all-cause mortality [39].
- Double beta-lactams are usually avoided because of overlapping toxicities. One exception is the combination of aztreonam with a beta-lactam; this regimen is used in patients unable to tolerate an aminoglycoside.

Monotherapy — Monotherapy (ceftazidime, cefepime, meropenem, or imipenem, piperacillin tazobactam) is also frequently employed; clinical trials with ceftazidime, imipenem cilastatin, or meropenem, demonstrated equivalent outcomes compared to two drug regimens [32,40,41]. The majority of the tested regimens provide coverage targeted at gram-negative bacilli, especially P. aeruginosa. Single drugs have also been compared to each other in various clinical trials as illustrated below:

- In a prospective study, treatment with meropenem was compared to ceftazidime in 411 patients and both drugs were found to be effective [42].
- Another prospective trial assessed cefepime versus imipenem as monotherapy for fever and neutropenia in 251 patients requiring hospitalization [43]. In an intent-to-treat analysis, the response to treatment in the two groups was comparable (68 versus 75 percent for imipenem versus cefepime) as was the side effect profile.
- A multicenter comparative study that assessed efficacy and safety randomly assigned 528 febrile neutropenic patients to piperacillin tazobactam (4.5 g every six hours) or cefepime (2 g every eight hours) [44]. In multivariate analysis, treatment with piperacillin-tazobactam was independently associated with treatment success (odds ratio, 1.65; 95% CI, 1.04-2.64).

One concern about monotherapy is the possibility that increasing antibiotic resistance in a number of pathogens may reduce the efficacy of this strategy. Single agents, especially ceftazidime, may actually promote the outgrowth of resistant organisms in this group of patients who require frequent antibiotic administration [45]. (See 'Antibiotic resistance' below.)

Addition of gram-positive coverage — Routine addition of gram-positive antibiotic coverage to the initial empiric antibiotic regimen has not been associated with significant clinical benefit [5,46-48]. A meta-analysis of seven randomized controlled trials found that the addition of gram-positive antibiotic coverage to standard empiric therapy did not reduce all-cause mortality in patients with cancer and febrile neutropenia [49].
Even in febrile neutropenic patients with skin and soft tissue infections who had a higher incidence of proven gram-positive bacteremia compared to patients with other infections (31 versus 17 percent), the addition of empiric vancomycin did not improve outcome and caused increased toxicity [50]. The risk of acquiring VRE is another reason to avoid empiric vancomycin use.

The addition of vancomycin should be considered in patients who present with hypotension, mucositis, skin or catheter site infection, history of MRSA colonization, or recent quinolone prophylaxis [51]. Vancomycin can also be considered for patients with clinical deterioration or persistent fever despite empiric antibiotics.

Linezolid is an alternative for patients intolerant to vancomycin. A multicenter, randomized, controlled study of 611 febrile neutropenic patients compared the safety and efficacy of linezolid and vancomycin [52]. Patients with proven or suspected infection due to a gram-positive pathogen were randomly assigned to receive linezolid (600 mg IV every 12 hours) or vancomycin (1 g IV every 12 hours) for 10 to 28 days. The following findings were noted:

- Clinical success rates seven days after completion of therapy were equivalent (87.3 percent compared to 85.2 percent with vancomycin)
- Mortality rates at 16 days after completion of therapy were similar (17 of 304 [5.6 percent] and 23 of 301 [7.6 percent] in the linezolid and vancomycin groups, respectively)
- Drug-related adverse events occurred more frequently in the vancomycin group (24 percent versus 17 percent for linezolid)
- Faster time to defervescence with linezolid in patients with documented gram-positive infections (5.9 ± 4.5 versus 9.1 ± 6.2 days with vancomycin), but no difference in those without documented infections
- Slower time to ANC >500 with linezolid, but only in those with known infections. No difference was observed in those without documented infections. Linezolid may cause myelosuppression, typically after two or more weeks of therapy. However, whether myelosuppressive effects can be seen earlier in patients receiving chemotherapy remains unknown [53,54].

Withdrawal of empiric vancomycin or linezolid should be considered after 72 hours if cultures remain negative [1].

Duration of antibiotic therapy — If an infectious source of fever is identified, antibiotics should be continued for at least the standard duration, eg, 14 days for E. coli bacteremia. With no known source, the timing of the discontinuation of antibiotics is usually dependent on resolution of fever and neutropenia. If the ANC increases to >500 cells/microL and the
patient becomes afebrile, antibiotics may be stopped, although some recommend treating for a minimum of seven days.

If the fever resolves and the patient remains neutropenic, it is less clear when antibiotics can be discontinued. Some experts recommend stopping antibiotics after early signs of hematologic recovery, but patients should be followed closely for recurrence of constitutional symptoms.

If fever persists after five to seven days, the choice of antibiotics should be reassessed, and empiric antifungal therapy is usually started.

A switch of intravenous antibiotic therapy to appropriate oral agents with broad-spectrum coverage can be considered in patients who have an identifiable cause of fever (eg, a urinary tract infection with E. coli) and improved rapidly, after their neutropenia has resolved.

Addition of antifungal drugs

Indications — The incidence of fungal infection (especially those caused by Candida or Aspergillus spp) rises after patients have experienced more than seven days of persistent fever and neutropenia [26,36,55]. Antifungal therapy is routinely added after five days of neutropenia in patients with persistent fever in whom reassessment does not yield a cause [1]. The rationale for this approach is that undiagnosed fungal infection may be present in many patients who die during periods of neutropenia [55]. In patients who are clinically unstable or have a suspected fungal infection, antifungal therapy should be considered even earlier than what is recommended for empiric therapy. (See "Treatment of candidemia and invasive candidiasis in adults" and "Treatment of invasive aspergillosis".)

An ongoing question is whether all neutropenic patients with persistent fever need to receive empiric antifungal therapy, since fungal infection is never documented in most patients. The following observations are relevant to this issue:

- In an autopsy study of patients who died after prolonged febrile neutropenia between 1966 and 1975, 69 percent of patients had evidence of systemic fungal disease [26]. It should be noted that over half of the patients in this early series had Candida infections, which may have been effectively prevented with antifungal prophylaxis strategies.
- Resolution of fever occurs in approximately 40 to 50 percent of patients given antifungal therapy (although this does not prove that the patient had an occult fungal infection) [27,56].
Several strategies have been suggested to try to identify those patients most likely to benefit from antifungal therapy [56]:

- Earlier diagnosis of fungal infection with improved diagnostic assays. (See "Clinical features and diagnosis of invasive aspergillosis", section on 'Galactomannan antigen detection'.)
- Identifying patients at low risk who might not require antifungal therapy [57].

Choice of drug — The field of antifungal therapy is evolving with several classes of drugs now available. Details regarding the efficacy of these drugs are presented below. In brief, if fever persists after five days of antibiotic therapy and reassessment does not yield a cause, the 2002 Infectious Diseases Society of America (IDSA) guidelines for the use of antimicrobial agents in neutropenic patients with cancer recommended adding amphotericin B with or without changing the antibiotics as one option [1]. However, these guidelines were published prior to trials showing the efficacy of voriconazole and caspofungin [58,59]. The 2009 IDSA guidelines for the management of candidiasis recommended either a lipid formulation of amphotericin B or caspofungin or voriconazole for empiric antifungal therapy in neutropenic patients [60]. We favor caspofungin because it appears to have equivalent efficacy but less toxicity compared with liposomal amphotericin B [56,59]. Other agents are preferred in patients with febrile neutropenia in whom there is a suspicion of invasive aspergillosis or other pulmonary mold infections. (See "Treatment of invasive aspergillosis".)

- **Amphotericin B** — Amphotericin B, often in a lipid formulation, has been the most common agent given. In a randomized trial, liposomal amphotericin B was compared to conventional amphotericin B in a composite of five end points: survival, resolution of fever during neutropenia, resolution of preexisting fungal infection, prevention of breakthrough fungal infection, and absence of premature discontinuation of the drug because of toxicity or lack of efficacy [61]. Both drugs performed similarly in terms of survival (93 versus 90 percent) and resolution of fever (58 percent each), but the liposomal preparation was associated with significant reductions in breakthrough fungal infections, infusion-related fever, chills, or rigors, and nephrotoxicity.

Based upon data from randomized trials, there is also increasing use of other effective, but less toxic drugs, such as voriconazole, caspofungin, and itraconazole [58,59,62]. The following trials illustrate the relative efficacy of these drugs:

- **Voriconazole** — An international open-label, randomized trial compared liposomal amphotericin B to voriconazole in 837 patients with persistent fever while neutropenic [58]. Mortality did not differ between the groups. There was a trend toward a better response with liposomal amphotericin B compared to voriconazole.
in four of five composite endpoints, including overall response (30.6 versus 26 percent), but voriconazole was associated with fewer documented breakthrough fungal infections (1.9 versus 5 percent). Voriconazole was associated with fewer infusion-related adverse effects and less nephrotoxicity but with more cases of transient visual changes and hallucinations.

The results of this study are difficult to interpret and may have been affected by the open-label design [63]. More patients had voriconazole stopped for perceived lack of efficacy (ongoing fevers), although fevers persisted equally in the liposomal amphotericin B group. The United States Food and Drug Administration (FDA) reviewed the results of the clinical trial along with additional information from the sponsor of the trial and recommended not to approve voriconazole for empiric antifungal treatment, as voriconazole did not fulfill criterion for noninferiority to liposomal amphotericin B [64,65]. Whether the failure to meet the statistical definition of noninferiority reflects a true difference in efficacy between voriconazole and liposomal amphotericin B or a problem in the study design awaits further clinical trials.

- **Caspofungin** — Another randomized controlled trial compared caspofungin to liposomal amphotericin B in 1095 patients with neutropenia and persistent fever despite four days of empiric antibiotic therapy [59]. The overall success rates (33.9 and 33.7 percent), and the rates of breakthrough fungal infections and resolution of fever were similar in both arms.

In the small subset of patients who had a fungal infection at baseline (only 27 per group), a successful outcome was significantly more likely with caspofungin versus liposomal amphotericin (52 versus 26 percent). Caspofungin was also associated with a significantly higher rate of survival seven days after the completion of therapy (92.6 versus 89.2 percent) and was significantly less likely to be associated with nephrotoxicity (2.6 versus 11.5 percent), infusion-related events (35 versus 52 percent), or cessation of therapy for drug-related adverse events.

Based upon susceptibility, efficacy, and safety data, we recommend caspofungin as first-line empiric therapy in patients with suspected fungal infections due to persistent fever [56,59]. Micafungin or anidulafungin could be used as alternatives to caspofungin, as the spectrum and antifungal activity of all three agents is similar. Micafungin appeared to be effective in small studies in patients with neutropenia [66,67]. However, these drugs have not been adequately studied or approved by the FDA for this indication. (See "Treatment of candidemia and invasive candidiasis in adults", section on 'Echinocandins'.)

For patients with suspected invasive fungal infections, such as those with documented pulmonary nodules, alternative agents should be used due to higher failure rates with caspofungin in preventing and treating aspergillosis [68]. Voriconazole or liposomal
Amphotericin should be used for empiric therapy in such patients. Current data are insufficient to conclusively determine which of these drugs is optimal; the choice of initial antifungal agents may vary based on an institution's experience (ie, epidemiology and susceptibility patterns) and patient risks for specific mold infections (eg, Aspergillus versus Zygomycetes).

It is also important to remember that caspofungin and other echinocandins are not active against Cryptococcus neoformans, Trichosporon, Fusarium, and filamentous molds, and have reduced activity against some yeasts (C. parapsilosis, C. rugosa, C. guilliermondii, and non-candidal yeasts). Failure of caspofungin to prevent aspergillosis has been reported [68]. Also, the clinical efficacy of the echinocandins for endemic fungi (Histoplasma, Blastomyces, Coccidioides spp) has not been demonstrated. (See "Treatment of cryptococcal meningoencephalitis and disseminated infection in HIV seronegative patients" and "Diagnosis and treatment of disseminated histoplasmosis in non-HIV-infected patients").

- **Micafungin and anidulafungin** — Micafungin or anidulafungin could be used as alternatives to caspofungin since the spectrum and antifungal activity of all three agents is similar. However, these drugs have not been adequately studied or approved by the FDA for this indication. (See "Treatment of candidemia and invasive candidiasis in adults", section on 'Echinocandins'.)

- **Itraconazole** — A randomized, controlled trial compared intravenous followed by oral itraconazole to conventional amphotericin B for up to 28 days as empiric therapies in 384 febrile neutropenic patients [62]. Itraconazole was at least as effective as amphotericin B (response rate 47 versus 38 percent), and significantly fewer patients had drug-related adverse effects (5 versus 54 percent). The median duration of neutropenia in this study was 10 and 8 days, respectively, for the itraconazole and amphotericin groups; five breakthrough fungal infections were observed in each group.

Two factors may limit the utility of intravenous itraconazole: it should not be used in patients with an estimated creatinine clearance below 30 mL/min, and dosing in hepatic failure has not been well characterized. Itraconazole has negative inotropic properties and can induce or exacerbate CHF. It also has a number of drug interactions, most notably cyclosporine, quinidine, and HMG-CoA reductase inhibitors (eg, lovastatin). (See "Pharmacology of azoles").

- **Fluconazole** — Fluconazole is generally not recommended for empiric therapy, because of concerns about efficacy. Although some randomized trials have shown equivalent efficacy to amphotericin B [69,70], a meta-analysis of 16 randomized, controlled trials failed to demonstrate a benefit for fluconazole in preventing mortality or systemic fungal infections in non-BMT patients [71]. Superficial fungal
infections were reduced, while colonization, but not infection, with fluconazole-resistant fungi was increased.

Another concern is that fluconazole is ineffective against Aspergillus and certain yeast (eg, C. krusei and C. glabrata). A retrospective study of hematogenous candidiasis from the M. D. Anderson Cancer Center found increasing isolation of C. krusei and C. glabrata infection; fluconazole prophylaxis appeared to be significant in promoting this trend [72].

CATHETER REMOVAL — In addition to antibiotics, catheter removal is recommended for patients with catheter-related candidemia or bacteremia in which one of the following organisms is implicated: S. aureus, Pseudomonas species, fast-growing atypical mycobacteria, Stenotrophomonas species, Bacillus species, or Corynebacterium jeikeium [18]. (See "Treatment of intravascular catheter-related infections", section on 'Removal'.)

Some authorities have suggested that catheter removal may not be necessary in neutropenic patients with candidemia, in whom the source is often the gastrointestinal tract rather than the central venous catheter. This is discussed in detail separately. (See "Treatment of candidemia and invasive candidiasis in adults", section on 'Catheter removal'.)

The Infectious Diseases Society of America (IDSA) clinical practice guidelines for the management of intravascular catheter–related infections can be accessed through their web site [73].

LOW RISK NEUTROPENIA — Patients with fever and neutropenia are always treated with the utmost urgency with intravenous broad-spectrum antibiotics. However, it has become evident that neutropenic cancer patients are not a homogeneous group and they have a variable risk of complications [7,57,74].

Predictors of risk — Outpatient antibiotic treatment may be offered to low risk patients [19,21]. Identification of candidates for this approach has been accomplished through the establishment of risk prediction rules [75]. The success of this approach depends upon careful patient selection, the use of appropriate antimicrobial agents, close monitoring, and an appropriate infrastructure (table 3) [19].

Models have been developed in an attempt to identify low risk patients [74]. Factors evaluated in these scoring systems have included severity of symptoms, presence of hypotension, history of chronic pulmonary disease, presence of solid tumor, absence of previous fungal infection, and age. One such model was derived prospectively and then validated in a separate cohort [57].

A number of randomized trials have examined the feasibility of outpatient management for patients with low-risk febrile neutropenia [76-79]. However, ensuring that truly low-risk
patients are selected appropriately is problematic. As a result, it is best to reserve outpatient management for centers with considerable experience in identifying patients at low risk for complications; the outpatient strategy should NOT be viewed as the current standard of care for febrile neutropenic patients.

Oral antibiotics — One approach to the management of these patients is the use of oral rather than parenteral therapy [74,78,80-82]. Two carefully designed trials compared ciprofloxacin and amoxicillin-clavulanate to ceftazidime or ceftriaxone plus amikacin, respectively, in low risk hospitalized neutropenic patients.

- In the larger trial from the European Organization for Research and Treatment of Cancer (EORTC), 312 patients with an ANC <1000/microL that was expected to resolve within ten days were randomly assigned to receive ciprofloxacin (750 mg PO twice daily) plus amoxicillin-clavulanate (625 mg PO three times daily) or standard doses of intravenous ceftriaxone plus amikacin [80]. The two regimens were associated with an equivalent rate of a successful outcome (86 versus 84 percent overall and 54 versus 50 percent in patients with microbiologically documented infections (54 versus 50 percent)). Three patients died in the group receiving oral therapy versus five in the parenteral treatment arm.
- The second trial was both randomized and double-blind with dummy oral or intravenous treatment; ciprofloxacin (30 mg/kg PO three times daily to a maximum dose of 750 mg three times daily) plus amoxicillin-clavulanate (40 mg/kg PO three times daily to a maximum of 500 mg three times daily) was compared to ceftazidime in 116 patients with ANC <500/microL [81]. The rate of successful treatment, without the need for modification of therapy, was similar in the two groups (71 versus 67 percent). There were no deaths.

An accompanying editorial emphasized that neither study addressed the safety of outpatient oral treatment [83], which would have the potential advantages of lower cost, a lesser risk of nosocomial infection, and a better quality-of-life [74]. The IDSA guidelines recommend consideration of oral ciprofloxacin plus amoxicillin-clavulanate only in low-risk patients [1].

The safety of oral outpatient therapy for appropriately selected low-risk patients has been addressed in three reports:

- A pilot study of 40 low-risk cancer patients (with breast cancer or sarcoma) evaluated the use of once daily, oral gatifloxacin (400 mg) for empiric treatment of febrile neutropenia [84]. The patients enrolled were in Risk Group 4 (clinically stable outpatients with no concurrent comorbidity) [85,86]. Ambulatory management with gatifloxacin was successful in 38 of 40 patients. The two treatment failures included a patient with polymicrobial bacteremia and a patient
with cellulitis; both responded to alternative antibiotic therapy. No patient required hospital admission.

- In a prospective study, 178 patients with a first febrile neutropenic episode who were predicted to be at low risk for complications were treated orally with **ciprofloxacin** plus **amoxicillin-clavulanate** and discharged if they were clinically stable or improving after an initial observation period [87]. Seventy-nine patients (44 percent) were discharged early (median time to discharge 26 hours). No serious medical complications occurred in the early discharge patients, however, three patients required readmission for an overall success rate of 96 percent.

- In a retrospective analysis, a single episode of febrile neutropenia was chosen from each of 712 consecutive outpatients with solid tumors who had been managed according to a prospective clinical pathway for low-risk febrile neutropenia (table 3) between 1997 and 2003 [88]. Outcomes and costs for 529 patients who were managed as outpatients were compared to those of 123 who were ineligible for outpatient care based on psychosocial criteria (eg, lacking access to a caregiver, telephone or transportation, residence >30 minutes from the treating center, poor compliance with prior outpatient therapy).

Outcomes were comparable in low-risk outpatients and low-risk inpatients in terms of response to initial antibiotics, overall success of therapy, serious complications (<1 percent in both groups) and mortality (no deaths in either group). Overall, 21 percent of those initially treated as outpatients subsequently required hospitalization. The mean costs of therapy among inpatients was double that of outpatients ($15,231 versus $7,772).

Another way to manage low-risk patients with febrile neutropenia is a "stepdown" approach, which has been used successfully by experienced centers even in patients at increased risk [89,90]. Patients are initially treated with parenteral therapy and then switched to an oral regimen, such as **ciprofloxacin** with or without **fluconazole** [89,90].

**COLONY STIMULATING FACTORS** — In one meta-analysis of 13 studies, colony stimulating factors (CSF) were shown to reduce the duration of neutropenia and length of hospitalization [91]. However, CSF have not been shown to decrease mortality and beneficial effects are quite modest. Thus, these agents should not be used routinely for patients with fever and neutropenia. (See "Prophylaxis of infection during chemotherapy-induced neutropenia".)

Special circumstances where the use of CSF may be considered include:

- Critically ill patients such as those with pneumonia, hypotension, or organ dysfunction.
- Patients whose bone marrow recovery is expected to be especially prolonged.
ANTIBIOTIC RESISTANCE — Of great concern has been the increasing frequency of antibiotic resistant organisms [77]:

- Among gram-positive organisms, these pathogens include coagulase negative staphylococci, methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), and penicillin (ceftriaxone)-resistant S. pneumoniae and streptococci.
- Gram-positive organisms that have intrinsic resistance to vancomycin (Leuconostoc, Lactobacillus, and Pediococcus)
- Multidrug resistant gram-negative rods, such as P. aeruginosa, Escherichia coli, and species of Citrobacter, Acinetobacter and Stenotrophomonas [19]. The use of fluoroquinolones for prophylaxis has contributed to the emergence of antibiotic resistance.
- The presence of extended spectrum beta-lactamases (ESBL) and plasmid-mediated AmpC-type beta lactamases can severely limit treatment options [18,19]. (See "Extended-spectrum beta-lactamases".

It is important to be aware of institutional resistance patterns since a variety of nosocomial outbreaks in cancer patients have also been reported. Some centers have reported an increased incidence of resistant pathogens such as Candida krusei with the routine use of prophylactic antibiotics and antifungals [78,80,81]. Antibiotic history, recent culture results, exposure to prophylactic antibiotics, and the susceptibility patterns for organisms in the institution should be used to help guide selection of initial antibiotic therapy.

Strategies to reduce drug resistance include limiting prophylaxis, using targeted therapy when feasible, discontinuing empiric therapies (eg, vancomycin) when cultures remain negative, and initiation of antibiotic restriction programs [19]. (See 'Addition of gram-positive coverage' above.)

PREVENTION

Colony-stimulating growth factors — Routine administration of myeloid growth factors for prophylaxis in previously untreated patients is not recommended for most chemotherapeutic regimens by the American Society of Clinical Oncology or the Infectious Diseases Society of America. Guidelines recommend the use of colony-stimulating growth factors with chemotherapeutic regimens that are associated with a high incidence of febrile neutropenia. (See "Prophylaxis of infection during chemotherapy-induced neutropenia").

Antibiotic prophylaxis — Many investigators have sought to determine if the administration of prophylactic antibiotics has a beneficial effect on clinical outcomes. Results have been mixed with respect to effectiveness and have aroused concern about side effects and antimicrobial resistance [92].
A meta-analysis was performed of 95 randomized, controlled trials in afebrile neutropenic patients (most of whom had hematologic cancers) comparing antibiotic prophylaxis with placebo or another antibiotic class with the following significant results [93]:

- Antibiotic prophylaxis significantly decreased the risk for death when compared with placebo or no treatment (relative risk, 0.67).
- Fluoroquinolone prophylaxis reduced the risk for all-cause mortality (relative risk, 0.52), as well as infection-related mortality, fever, clinically documented infections, and microbiologically documented infections.
- Fluoroquinolone prophylaxis increased the risk for colonization with resistant bacteria, but these results were not statistically significant.
- All prophylactic antibiotics were associated with an increased risk for adverse events.

Subsequent to this meta-analysis, two large, randomized, double-blind placebo-controlled trials of prophylactic fluoroquinolone therapy in patients undergoing cancer chemotherapy were performed [94,95]. The populations in both trials consisted primarily of patients with solid tumors or hematologic malignancies who were at high risk for severe and prolonged neutropenia. The first trial evaluated a higher risk patient population, mainly inpatients, who received levofloxacin from the time of initiation of chemotherapy until engraftment [94]. The second trial was in the outpatient setting, and levofloxacin was administered for the seven days estimated to coincide with the nadir of the white cell count [95]. The primary end-point for both trials was the occurrence of fever. These studies demonstrated the following results:

- Prophylactic antibiotics led to a significant decrease in febrile episodes.
- Neither trial documented a survival benefit associated with antibiotic prophylaxis.
- The inpatient study demonstrated that the levofloxacin-treated group had a lower rate of Escherichia coli bacteremia than did the placebo group (1.2 percent versus 3.0 percent). However the use of prophylaxis was associated with significantly higher rates of antimicrobial resistance (77 percent versus 17 percent).

The Infectious Diseases Society of America does not endorse routine prophylaxis for neutropenic patients. The authors of the meta-analysis cited above recommend that prophylaxis should be considered in patients with hematologic cancer, since they are at higher risk compared to neutropenic patients with solid tumors. Others have suggested that in light of significant resistance issues, efforts to improve patient risk stratification will be critical to minimize unnecessary use of antimicrobial agents and to preserve their efficacy. We agree with the IDSA guidelines and also do not routinely recommend quinolone antibiotics prophylaxis, but consider it on a case by case basis.

SUMMARY AND RECOMMENDATIONS
General principles

- Fever and neutropenia is a medical emergency requiring prompt administration of broad-spectrum antibiotics. (See 'General treatment principles' above.)
- The incidence of an occult infection in a febrile neutropenic patient increases with the severity of the neutropenia. Morbidity and mortality is also increased in patients with profound neutropenia (ANC <100/microL). (See 'Predisposing factors' above.)
- Contributory factors to the pathogenesis of febrile neutropenia include the direct effects of chemotherapy on mucosal barriers and immune deficits related to the underlying malignancy. (See 'Pathogenesis' above.)

Pathogens

- An infectious source is identified in only approximately 30 percent of febrile neutropenic episodes. Although gram-negative organisms predominated a few decades ago, more infections are now documented to be gram-positive organisms. Factors contributing to this trend include use of long-term indwelling lines and empiric and prophylactic antimicrobials that are primarily active against gram-negative pathogens. (See 'Associated pathogens' above.)
- Viral infections, especially human herpes viruses, and fungal pathogens are also common in this patient population.

Initial evaluation

- A thorough general physical examination should be performed to locate the source of infection; in the absence of neutrophils, signs of inflammation can be extremely subtle. Review of symptoms and a physical examination should be repeated daily. (See 'Patient evaluation' above.)

Empiric antibiotic therapy

- Patients with cancer who present with fever and neutropenia should be treated immediately with empiric broad-spectrum antibiotics. (Grade 1A)
- Initial antibiotic selection should be guided by the patient's history, allergies, symptoms, signs, recent antibiotic use and culture data, and awareness of institutional nosocomial infection patterns. Ideally, antibiotics should be bactericidal and should be administered through alternate ports of any indwelling intravenous line. (See 'Empiric Therapy' above.)
- There is no clear optimal choice for empiric antibiotic therapy. Combination therapy and monotherapy have led to similar outcomes. We recommend the use of monotherapy with cefepime or carbapenem as initial therapy (Grade 2A). In more critically ill patients, we suggest the addition of an aminoglycoside for better gram-
negative coverage (Grade 2B); in critically ill patients with renal insufficiency, we suggest the use of a fluoroquinolone or aztreonam instead (Grade 2C).

- Antibiotic therapy should be altered if there is evidence of progressive disease or a new complication.
- We do NOT recommend the routine use of gram-positive antibiotic coverage (eg, vancomycin or linezolid) (Grade 1A). However, we do recommend the addition of vancomycin or linezolid in the following circumstances: presence of hypotension, mucositis, skin or catheter site infection, history of MRSA colonization, recent quinolone prophylaxis, or overall clinical deterioration. (See 'Addition of gram-positive coverage' above.)

Duration of antibiotic therapy

- If an infectious source of fever is identified, antibiotics should be continued for the standard duration for that particular pathogen and site of infection.
- In the patient with no known source, the timing of the discontinuation of antibiotics is usually dependent upon resolution of fever and neutropenia. We suggest that antibiotics be stopped if the ANC increases to >500/microL and the patient becomes afebrile (Grade 2C). (See 'Duration of antibiotic therapy' above.)
- In the patient without an identified source who becomes afebrile but remains neutropenic, we suggest treatment for a total of 14 days with careful follow-up on discontinuation of therapy (Grade 2C).
- In the patient with an identifiable source who improves on antibiotic therapy, we suggest switching to an appropriate oral agent for completion of the antibiotic course.

Empiric antifungal therapy

- We recommend the addition of an antifungal agent in neutropenic patients with no obvious source of infection who are persistently febrile for five days despite broad-spectrum antibacterials (Grade 1A). We recommend adding caspofungin as first-line antifungal therapy (Grade 1B). (See 'Addition of antifungal drugs' above.)

Catheter removal

- In addition to antibiotics, we recommend catheter removal for patients with catheter-related candidemia or bacteremia in which one of the following organisms is implicated: S. aureus, Pseudomonas species, fast-growing atypical mycobacteria, Stenotrophomonas species, Bacillus species, or Corynebacterium jeikeium. (See "Treatment of intravascular catheter-related infections", section on 'Removal'.)

Low risk patients
Outpatient or oral antibiotic therapy is a reasonable option for patients with low-risk febrile neutropenia who meet all of the requirements for safe and successful outpatient management (table 3). We suggest that this approach be limited to centers with considerable experience in the identification, treatment, and monitoring of low-risk patients.

Use of prophylactic antibiotics

- We do NOT recommend the routine use of prophylactic antibiotics. (See 'Prevention' above.)

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REFERENCES

22. Coullioud, D, Van der Auwera, P, Viot, M, Lasset, C. Prospective multicentric study of the etiology of 1051 bacteremic episodes in 782 cancer patients. CEMIC (French-Belgian Study Club of Infectious Diseases in Cancer). Support Care Cancer 1993; 1:34.
41. Cometta, A, Calandra, T, Gaya, H, et al. Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empiric therapy for fever in


49. Aoun, M. Review: Additional anti-gram-positive antibiotics do not reduce all-cause mortality in cancer and febrile neutropenia. ACP J Club 2006; 144:3.


INTRODUCTION — Infection is a major cause of morbidity and mortality in cancer patients [1]. Fever may be the first manifestation of a life-threatening infection, particularly during periods of neutropenia. Febrile episodes occur in approximately one-third of neutropenic episodes in children with chemotherapy-induced neutropenia or after hematopoietic stem cell transplantation [2]. The rate of occurrence is 0.76 episodes per every 30 days of neutropenia.

The demonstration of markedly reduced infection-related morbidity and mortality with the empiric use of broad-spectrum antibiotics during periods of febrile neutropenia was a major advance in the field of oncology in the 1970s [3,4]. Subsequent studies identified factors associated with a higher risk of bacterial infection and facilitated a more tailored approach to empiric therapy.

Because of important differences between oncology and hematology patients with neutropenia, fever in the pediatric cancer patient during periods of therapy-induced neutropenia are reviewed here. The types of infections and management of fever in the child with other forms of neutropenia are discussed separately. (See "Risk of infection in children with non-chemotherapy-induced neutropenia" and "Management of fever in children with non-chemotherapy-induced neutropenia".)

DEFINITIONS OF NEUTROPENIA — Neutropenia is strictly defined as an absolute neutrophil count (ANC) <1500/microL. The ANC is calculated using the following formula:

\[
\text{ANC} = \frac{\text{total white blood cell count (cells/microL) x (percent neutrophils + percent bands)}}{100}
\]

For purposes of management of the febrile pediatric cancer patient, neutropenia is defined as an ANC <500/microL or an ANC <1000/microL with a predicted decline to ≤500/microL [5,6]. The relative risk of infection is related to both the degree and duration of neutropenia. An increased risk becomes apparent at an ANC <1000/microL, is greater at
an ANC ≤500/microL and greatest at an ANC ≤100/microL [2,7]. Patients with neutropenia projected to last for more than 10 to 14 days also are at a higher risk of infection than are those with neutropenia of shorter duration. Other factors that predispose to infection in association with chemotherapy include breakdown of skin and mucosal barriers, such as mucositis following methotrexate treatment, and altered humoral and cellular immunity [8].

Although infections are more common in the pediatric cancer patient during periods of chemotherapy-induced neutropenia, they also can occur in the absence of neutropenia. For example, 90 percent of pediatric oncology patients have central venous catheters, which may be a source of infection at all times. Because children are not always able to convey localized complaints, the pediatric oncology patient with fever must be evaluated regardless of the ANC.

DEFINITIONS OF FEVER AND MEASUREMENT OF TEMPERATURE — Fever generally is defined as a single oral temperature >38.3ºC (101ºF) in neutropenic patients [9]. A temperature ≥38ºC (100.4ºF) for longer than one hour or two elevations >38ºC during a 12-hour period are other definitions of fever that are used [5,10]. Measuring the temperature orally is preferable, although an axillary temperature is acceptable if the patient is unable to use an oral thermometer. Generally, no conversion is made between axillary and oral temperatures. However, more conservative guidelines suggest that adding 0.5ºF (0.3ºC) to the axillary temperature reading may be warranted. Because of associated risks of mucosal trauma and bacteremia, measurement of rectal temperature should be avoided in neutropenic patients.

Fever often is the sole sign of occult infection in the neutropenic host. However, this sign may be absent in some infected patients who instead may be hypothermic, hypotensive, listless, or confused. Thus, infection must be considered and treated empirically if any signs of clinical deterioration are present in a neutropenic child, regardless of the recorded temperature.

CAUSES OF FEVER IN THE NEUTROPENIC CANCER PATIENT — The rate of documented infection, when a child presents with fever and therapy-induced neutropenia, ranges between 10 and 40 percent [2,11-13]. No clinical or microbiologic evidence of infection will be established in the remainder. Bacteremia is the most common form of documented infection [2,13].

- In one retrospective study of 337 episodes of febrile neutropenia in children during 2004-2005, a pathogen was identified in 86 (25 percent), and among those, 54 (63 percent) were bacterial and 41 (48 percent) were bacteremias [13]
- In a prospective study of 115 episodes of fever and neutropenia in 72 children, 21 percent of the episodes were associated with positive blood cultures [12].
Both gram-positive and gram-negative organisms are isolated frequently from the blood in febrile neutropenic children [2,13,14]. The most common gram-positive pathogens are coagulase-negative staphylococci, viridans streptococci, and Staphylococcus aureus [2,13]. Aerobic gram-negative bacilli account for approximately one-third to one-half of bacteremic episodes, with Escherichia coli, Klebsiella sp., Pseudomonas sp., Acinetobacter sp., and Enterobacter sp. among the more common isolates [2,11-14].

Fungi, typically Candida sp., are more likely to be recovered after prolonged courses of broad-spectrum antibiotics but occasionally may be the primary pathogen [2]. Other potential fungal organisms include Aspergillus sp., Phycomycetes, and Cryptococcus sp. [15,16]. Fusarium sp. also have been increasingly recognized in these hosts [17]. The most significant viral etiologies are Herpes simplex and varicella-zoster virus [13,18,19]. Respiratory viruses are also frequently detected in nasopharyngeal aspirates [13,18,20]. In addition to bacteremia, other sites of infection include the gastrointestinal tract, with oral or intestinal mucositis or diarrhea caused by organisms such as Clostridium difficile and Salmonella; upper and lower tract respiratory tract; urinary tract; and skin and soft tissues [1,11].

EVALUATION — Because of the substantial risk of a life-threatening infection in the febrile neutropenic child, the initial evaluation must be conducted promptly.

Physical examination — A careful physical examination should be performed with particular attention paid to those sites most commonly infected, including:

- Skin, especially folds, areas surrounding nail beds, central venous line exit sites and subcutaneous tunnel, if present, and sites of bone marrow aspiration and lumbar puncture
- Sinuses
- Oropharynx, with attention to the gingiva
- Lungs
- Abdomen
- Perineum, particularly the perianal and labial regions

Mild erythema or tenderness should not be ignored because signs of inflammation in the neutropenic patient may be subtle. Repeated physical examinations are essential. Visual signs of inflammation may become evident only when neutrophil counts are recovering.

Cultures — Blood cultures should be obtained without delay. Blood cultures should be taken from the central line when such access is available. Opinions vary as to whether blood should be cultured from peripheral sites, as well [21-23]. The rationale for culturing blood from both peripheral and central sites is to differentiate a catheter-related infection from a bacteremia from another source. However, peripheral cultures may be positive with
significant central catheter-related infections [24], and, for cancer patients, treatment recommendations for central catheter-related infections and for bacteremias from other sources are the same. Thus, unless contrary institutional practice guidelines are in place, we do not recommend the routine culturing of blood from peripheral sites in addition to central sites.

Obtaining more than one blood culture is helpful in the interpretation of blood culture results. If coagulase-negative staphylococci are isolated from two or more blood cultures, true bacteremia caused by this organism is more likely to exist than contamination of the specimen that may be reflected by a single positive blood culture for this organism. When obtaining blood from a central venous catheter, the importance of sampling all lumens is supported by studies in which 32 to 43 percent of positive cultures from double lumen catheters were positive from only one of multiple lumens [21,25].

In addition to the blood, the only other site that may be useful to culture routinely is urine in febrile, neutropenic girls. In one study, urinary tract infections accounted for 11 percent of all documented infections in febrile neutropenic patients, and 76 percent of those occurred in girls [1]. Additional studies should be obtained only as clinically indicated. Examples include:

- Chest radiographs in children with respiratory signs and symptoms [26,27]. A chest radiogram that is negative for infiltrates should be interpreted with caution because infiltrates might appear with a delay or only when neutrophil counts are recovering.
- Abdominal radiographs and/or ultrasonography in children with abdominal signs and symptoms, particularly abdominal pain
- Lumbar puncture for altered mental status or meningeal signs
- Stool culture, Clostridium difficile toxin, ova, parasites, and viral cultures in patients with diarrhea
- Culture and Gram stain of drainage from any site with drainage

EMPIRIC PARENTERAL ANTIBIOTICS — The cornerstone of therapy for the febrile, neutropenic patient is prompt initiation of empiric broad-spectrum antibiotics. General guidelines have been published for the use of empiric antibiotics during episodes of fever and neutropenia, including those published by the Infectious Diseases Society of America (IDSA), most recently updated in 2002 [5]. These guidelines emphasize that, when choosing empiric therapy, each practitioner should consider:

- The presence or absence of low-risk factors (eg, initial absolute monocyte count of ≥100 cells/microL, no comorbidity, and a normal chest radiograph)
- The types of bacterial isolates found in the institution
- Antibiotic susceptibility patterns
- Drug allergies of the patient, if any
Presence of organ dysfunction, particularly renal and hepatic
The particular chemotherapeutic regimen and when it was administered: for example, an association exists between viridans streptococcal infection and high-dose cytarabine therapy [28,29]
Whether the patient was receiving prophylactic antimicrobials

As discussed above, bacterial infections in neutropenic cancer patients may be caused by either gram-positive or gram-negative organisms, and thus, empiric antibiotic therapy must be effective against a broad spectrum of potential pathogens.

Monotherapy — Although combination therapy once was the standard of care for all febrile neutropenic cancer patients, many studies have demonstrated that monotherapy with a broad-spectrum antipseudomonal agent (such as cefepime or ceftazidime) or a carbapenem (imipenem-cilastatin) is as efficacious as combination therapy for the empiric treatment of most patients [30-32]. Consequently, monotherapy is now considered a standard therapy for uncomplicated episodes of fever [5,6].

Monotherapy regimens:

- **Cefepime** — 50 mg/kg intravenously (IV) every 8 hours up to a maximum of 2 g per dose; OR
- **Ceftazidime** — 50 mg/kg IV every 8 hours up to a maximum of 2 g per dose; adjust dose for renal dysfunction; OR
- **Imipenem-cilastatin** — 25 mg/kg IV every 6 hours up to a maximum of 1 g per dose for infants older than one month of age and children; adjust dose for renal dysfunction

Combination therapy — The alternative to monotherapy is combination therapy with an aminoglycoside (eg, gentamicin) plus an antipseudomonal penicillin (eg, ticarcillin with clavulanate), cefepime, ceftazidime, or a carbapenem [5]. Potential advantages of combination therapy for the patient at high risk for bacterial infection include synergistic effects against some gram-negative and gram-positive organisms and possible reduction in the emergence of resistant organisms during treatment. The major disadvantage of combination therapy is the toxicity, particularly nephrotoxicity, of aminoglycosides. Substantial efforts have focused on modifying the dose schedule of aminoglycosides to achieve a better toxicity profile or eliminating aminoglycosides from empiric antibiotic regimens altogether. While such efforts are promising, larger studies are warranted before changing the currently available guidelines.

A sample combination therapy regimen is:
- **Gentamicin** — 2.5 mg/kg per dose (for patients ≤50 kg) or 1.5 to 2 mg/kg per dose (for patients >50 kg) IV every 8 hours up to a maximum of 120 mg per dose; adjust dose per serum concentrations and for renal dysfunction; PLUS
- **Ticarcillin-clavulanate** — 75 mg/kg per dose IV every 6 hours up to a maximum of 3.1 g per dose; adjust dose for renal dysfunction

If abdominal symptoms are present, particularly abdominal pain or blood per rectum, the addition of metronidazole should be considered if the initial combination therapy does not adequately cover anaerobic organisms [6].

For those patients in whom a site of infection is defined, therapy can be adjusted from broad-spectrum to the most appropriate treatment for the particular infection once the patient has become afebrile [5].

Vancomycin — **Vancomycin** is a logical drug to include in a broad-spectrum regimen to improve coverage of gram-positive organisms, but the necessity of doing so has not been proven. Although up to two-thirds of bacterial isolates from blood in febrile neutropenic cancer patients are gram-positive cocci and are frequently coagulase-negative staphylococci resistant to extended-spectrum penicillins or third-generation cephalosporins, morbidity and mortality of infections have not differed between patients treated with or without vancomycin in the initial antibiotic regimen [33-35]. Infections with alpha-hemolytic streptococci may be an exception to this observation [36]. The use of vancomycin as part of empiric therapy of febrile neutropenia is further discouraged because administration of the drug increases the probability of colonization or infection with vancomycin-resistant enterococci (VRE). Among pediatric oncology patients, rates of VRE colonization have been reported to be as high as 30 percent [37,38], with an annual incidence of infection of 8 percent [37].

Efforts to decrease the emergence of VRE and the possible spread of vancomycin resistance to other gram-positive organisms, such as S. aureus, have been strongly encouraged. Many institutions have implemented guidelines for the use of vancomycin that have been recommended by the Hospital Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention (CDC) [39]. These restrictions include using vancomycin in febrile neutropenic patients only when a strong suspicion of infection with a gram-positive organism exists. Vancomycin is recommended in the 2002 guidelines from the IDSA for the following clinical scenarios [5]:

- Clinically suspected central venous line site infection
- Known colonization with methicillin-resistant S. aureus (MRSA), or penicillin- and cephalosporin-resistant Streptococcus pneumoniae
- When a blood culture has been reported to be growing gram-positive bacteria and identification and susceptibility testing are pending
Additional indications for vancomycin may include:

- Substantial mucositis
- Prophylaxis with quinolones during afebrile neutropenia
- Previous history of infection with penicillin-resistant streptococci
- Recent intensive chemotherapy associated with a high risk for infection with such organisms (eg, alpha-hemolytic streptococcal infection following high-dose cytarabine) [13]

Antifungal therapy — In patients with persistent fever and neutropenia despite empiric antibacterial therapy, concern for a clinically occult fungal infection must arise. As noted above, a variety of fungi can cause infection in cancer patients, and early diagnosis can be difficult. In a randomized, placebo-controlled trial, empiric intravenous administration of amphotericin B early in the course of febrile neutropenia was effective in the control of clinically occult fungal invasion and in the prevention of fungal superinfections [40]. Most oncologists begin empiric intravenous amphotericin B in patients who have remained febrile and profoundly neutropenic after receiving five to seven days of broad-spectrum antibiotics based upon this and subsequent corroborative studies [5].

Prior to initiating amphotericin B therapy, evaluations should be performed to determine whether systemic fungal infection exists (eg, radiographs of sinuses and CT of the abdomen and chest, and biopsy of any suspicious lesions) [5].

A sample amphotericin B dosing schedule is:

- 0.5 mg/kg per dose administered IV once daily for empiric therapy; 1.0 to 1.5 mg/kg per dose administered IV once daily for documented fungal infections.

Despite the potential benefits of empiric amphotericin B therapy, the substantial toxicity, particularly nephrotoxicity, that may accompany its administration limits its use in many patients. Consequently, potentially less toxic alternatives, including lipid formulations of amphotericin B, triazole derivatives (eg, voriconazole), and echinocandins (eg, caspofungin), are being studied. Four randomized control trials, which included 395 children, compared a lipid formation of amphotericin B (liposomal or amphotericin B colloidal dispersion [ABCD]) with conventional amphotericin B in patients with persistent fever and neutropenia [41-44]. Pooled analyses of these studies demonstrated that lipid preparations of amphotericin B were associated less nephrotoxicity than conventional amphotericin B, and liposomal amphotericin B was associated with less infusion-related toxicity than either ABCD or conventional amphotericin B [45]. No difference in breakthrough fungal infection was observed.
An alternative to amphotericin was studied in an open-label, prospective, randomized, multicenter trial of 849 patients, which included 33 children between the ages of 12 and 18 years. Patients with persistent fever and neutropenia after four days of systemic antibacterial therapy were randomized to initially receive either voriconazole (6 mg/kg IV every 12 hours on day one and then 3 mg/kg IV every 12 hours) or liposomal amphotericin B (3 mg/kg per day) [46]. The voriconazole group was reported to have had fewer documented breakthrough infections, fewer severe infusion-related reactions, and less nephrotoxicity, but did experience more transient visual disturbances and hallucinations than the liposomal amphotericin B group. Further analysis of this study, however, indicated that liposomal amphotericin B was significantly more effective than voriconazole and should be preferred [47].

The echinocandins are another class of antifungals that are being studied in this patient population. For example, a randomized, double-blind, multicenter trial compared the safety and efficacy of caspofungin to liposomal amphotericin B for empiric antifungal therapy in children with persistent fever and neutropenia [48]. Fifty-six children received caspofungin (70 mg/m2 loading dose on day one, then 50 mg/m2 daily [which could be increased to a maximum of 70 mg/m2 daily]), and 26 received liposomal amphotericin B (3 mg/kg daily). Drug-related clinical and laboratory adverse effects, including infusion-related toxicity and nephrotoxicity, were similar between the two groups. Favorable overall response rates were also similar, however, the study was not powered to detect statistically significant differences. Further study is indicated.

Duration of therapy — Recommendations have evolved over the past decade with respect to the duration of empiric antibiotic therapy and hospitalization for those febrile, neutropenic patients in whom no infectious etiology is identified. Previous studies had suggested that antibiotic therapy should continue until resolution of the neutropenia [49,50]. However, investigators have studied risk factors for the development of serious infection in an effort to reduce the length of time of hospitalization, if any, and the length of therapy in those children and adolescents with low risk for significant complications.

As an example, a prospective, multicenter study of 423 febrile neutropenia episodes in children was conducted to develop a scoring system to predict adverse events [51]. The investigators defined adverse events as serious medical complication as a result of infection, microbiologically defined infection (including viral infection), and radiologically confirmed pneumonia. Their scoring system incorporated preceding chemotherapy more intensive than acute lymphoblastic leukemia maintenance (weight = 4), hemoglobin >9 g/L (weight = 5), leukocyte count <3x10^3/L (weight = 3), and platelet count <50x10^3/L (weight = 3). They found a total weighted score of ≥9 predicted future adverse events. The predictive performance of the scoring system was best when applied to episodes where the adverse events were only apparent after reassessment following 8 to 24 hours of inpatient therapy. This resulted in 35 percent of the episodes being classified as low risk, with 92
percent sensitivity, 45 percent specificity, 93 percent negative predictive value, and 40 percent positive predictive value. This scoring system has yet to be validated prospectively.

Other investigators found in their retrospective study that chills, hypotension, requirement for fluid resuscitation, and a diagnosis of leukemia or lymphoma correlated with an increased probability of bacteremia [11]. Persistent fever and an ANC <100/µL after 48 hours of empiric therapy were associated with a high risk for complications. Based upon these findings, these investigators recommended that children who initially present without signs of sepsis and who are afebrile and have an ANC >100/µL after 48 hours of empiric therapy could be considered for early hospital discharge, with continuation of outpatient antibiotics [11]. This study did not address whether antibiotics could be safely discontinued prior to the resolution of neutropenia.

This approach also may apply to patients with prolonged neutropenia (ie, more than seven days) who generally are considered at relatively high risk for both bacterial and fungal infections. One study showed that these patients could be discharged safely before resolution of the neutropenia if they appeared well, were afebrile for at least 24 hours, had sterile blood cultures, had any local infection under control, and showed evidence of bone marrow recovery [52]. Bone marrow recovery was defined as any sustained increase in platelet count and ANC or absolute phagocyte count (APC = ANC + absolute monocyte count). In addition, these investigators showed that patients with either transient or prolonged neutropenia could be discharged safely from the hospital with antibiotics discontinued when they met the above criteria [52,53]. Studies such as these have led many groups to use similar criteria to guide decisions on the appropriate duration of therapy [9].

Evidence exists for discontinuation of antibiotics and discharge from the hospital prior to evidence of marrow recovery. Data from a small retrospective study suggests the safety of this approach for patients who are afebrile for at least 24 hours, are in good clinical condition, have been treated with intravenous antibiotics for a minimum of 72 hours, and have no identified infectious source [54]. A prospective analysis of this approach has yet to be reported.

COLONY STIMULATING FACTORS (CSFS) — Most children treated for cancer in the United States are treated on research protocols, and many of the intensive chemotherapy regimens incorporate the use of granulocyte-colony stimulating factor (G-CSF) immediately after courses of chemotherapy. Potential benefits of prophylactic G-CSF or granulocyte-monocyte colony stimulating factor (GM-CSF) include a reduction in the duration of neutropenia and, in theory, the risk of infection. (See "Prophylaxis of infection during chemotherapy-induced neutropenia".)

Although most pediatric studies have demonstrated that prophylactic use of G-CSF reduces the duration of neutropenia, conclusions about its impact on rates of febrile neutropenia,
days of fever, days of intravenous antibiotic use, rates of documented infection, and lengths of hospital stay have conflicted [55-59]. The conflicting results may reflect differences in the myelosuppressive intensity of the various chemotherapy regimens, one of many variables among the different studies. In a meta-analysis of 16 randomized, controlled pediatric studies of the prophylactic use of CSFs, CSFs were associated with a 20 percent reduction in febrile neutropenia and an approximately two-day decrease in hospitalization duration, but no difference in parenteral IV antibiotic therapy or infection-related mortality rate [60].

Significant benefits from initiating colony stimulating factors in the midst of febrile neutropenia have not been firmly established. In a double-blind, randomized study of 186 episodes of febrile neutropenia in pediatric cancer patients, a small but statistically significant reduction in the length of hospital stay (five versus seven days) and days of intravenous antibiotic use (five versus six days) was observed with administration of G-CSF [61]. In a different study, 66 patients with chemotherapy-induced febrile neutropenia (59 with acute lymphoblastic leukemia) were randomly assigned to treatment with antibiotic therapy with or without G-CSF. Patients treated with G-CSF had shorter median time to resolution of neutropenia (4 versus 13 days), but no significant differences in duration of fever or antibiotic treatment, addition of antifungal therapy, or incidence of shock [62].

Whether high-risk patients (see above) and/or those with predicted prolonged courses of neutropenia (ie, more than 10 days) might benefit from the use of G-CSF remains unanswered. Comparable, modest results were obtained in a study evaluating the effect of the addition of GM-CSF during episodes of fever and neutropenia [63]. Thus, at present, the routine initiation of G-CSF or GM-CSF for uncomplicated episodes of febrile neutropenia is not recommended [5,64]. For children with complicated episodes, interventional G-CSF may be appropriate [64,65].

**OUTPATIENT MANAGEMENT OF FEVER AND NEUTROPENIA —** Although the standard of care for all febrile neutropenic patients remains hospitalization and administration of parenteral empiric antibiotics, several studies using strict eligibility criteria now suggest that outpatient treatment may be safe and appropriate for those at low risk of serious infection.

- In a preliminary study, 19 patients meeting low-risk criteria were treated initially with an intravenous dose of ceftriaxone and then evaluated daily in an outpatient setting; they received additional doses of ceftriaxone if they remained febrile [66]. Eighteen of the patients were treated successfully as outpatients; one patient was admitted for persistent fever, but the outcome also was uncomplicated in this patient.
In another study, 73 episodes of fever and neutropenia in "low-risk" patients (representing 25 percent of all episodes in that period) were managed in the outpatient setting [67]. Enrolled patients received one dose of intravenous ceftazidime, after which they were randomized to continue parenteral ceftazidime via a portable infusion pump or to receive oral ciprofloxacin. The source of fever (bacteremia, cellulitis, and otitis media) was identified in 11 percent, including gram-positive and gram-negative bacteremia. Ultimately, 86 percent of episodes were managed entirely as outpatients; 14 percent required hospitalization, the majority for prolonged neutropenia, and none with complicated stays. There were no differences between the two groups of patients with respect to the duration of fever, neutropenia, treatment, or rates of hospitalization.

A larger study at St. Jude Children's Research Hospital determined that, following a course of intravenous antibiotics, oral cefixime was equivalent to continued parenteral antibiotics in "low-risk" febrile neutropenic episodes [68]. One hundred fifty-six patients (mean age six years) with 200 febrile neutropenic episodes were randomized after blood cultures were negative at 48 hours. Patients with suspected sites of infection, positive chest radiographs, positive surveillance cultures for MRSA or P. aeruginosa, hypotension, severe mucositis, or diarrhea were excluded. Treatment failure usually caused by recurrent fever occurred with equal frequency in the groups receiving cefixime or IV antibiotics (28 versus 27 percent); one patient receiving cefixime experienced breakthrough fever and grew cefixime-resistant E. coli from both ports of a central venous catheter, without accompanying positive peripheral blood cultures. Although the patients in this study remained hospitalized, the results suggest that the use of oral antibiotics could lead to earlier hospital discharge and outpatient management for low-risk patients.

A trial of outpatient ciprofloxacin versus ceftriaxone after 24 hours of ceftriaxone and amikacin in children, the majority of whom had hematologic malignancy, showed equivalent efficacy for the two regimens [69]. Characteristics of the study population differed from other reports in two major ways. Seventy percent of patients had a clinical site of infection (approximately 40 percent of which was rhinitis), a rate considerably higher than most other studies. In addition, only half of the patients had indwelling central venous catheters, a lower percentage than typically found at most institutions in the United States.

Two reviews have summarized the experience with outpatient management and outlines areas for further study [70,71].

TREATMENT RECOMMENDATIONS — Guidelines for initial empiric antibiotic selection have been adapted from the 2002 consensus summary of the IDSA (table 1A-B) [5]. However, they are only meant to be guidelines, and treatment must be individualized for each patient. Once initial empiric mono- or combination therapy has
been chosen for children, modification of the regimen must be considered based upon a variety of clinical scenarios, including:

- Change in clinical status or vital signs
- Persistent fever for more than 3 days
- Isolation of a blood-borne organism
- Development of signs or symptoms of a localized infection

An alternative algorithm was based upon a review of 27 prospective trials and five reviews of fever and neutropenia that included pediatric patients [72]. These authors suggest that patients who are well with no comorbidity at presentation of febrile neutropenia may be candidates for inpatient oral or outpatient parenteral antibiotic therapy, with anticipation of early discharge and discontinuation of therapy with signs of marrow recovery reflected in a rising ANC or APC. In the case of patients with either newly diagnosed or relapsed leukemia, data suggest that the APC should be >100/microL. Further carefully designed and controlled clinical trials are needed to validate this approach.

Many centers now will stop antibiotics after 48 hours of empiric therapy in a patient with no identified source of fever if that patient appears well, is afebrile for at least 24 hours, and shows evidence of bone marrow recovery.

Updated IDSA guidelines for empiric therapy for febrile neutropenic cancer patients are expected fall 2010.

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REFERENCES


rrophylaxis of infection during chemotherapy-induced neutropenia

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INTRODUCTION — Intensive cytotoxic chemotherapy often causes profound neutropenia, which may result in hospitalization for treatment of fever or cause potentially fatal infection [1]. In an attempt to decrease infectious complications, recombinant human granulocyte colony-stimulating factor (G-CSF, filgrastim) and granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim) have been used to reduce the duration and degree of neutropenia. Alternatively, prophylactic antibiotics have been administered to prevent the development of bacterial infections as a complication of the neutropenia.

The roles of the myeloid colony-stimulating factors (CSFs) and prophylactic antibiotics will be reviewed here. As will be seen, the data support their use only in selected high-risk patients. The management of patients with chemotherapy-induced neutropenia and fever are discussed elsewhere. (See "Fever in the neutropenic adult patient with cancer".)

DEFINITIONS

Neutropenia — 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 fraction of polymorphonuclear cells (PMNs) and band forms:

\[ \text{ANC} = \text{WBC (cells/microL)} \times \frac{\text{percent (PMNs + bands)}}{100} \]

Neutrophilic metamyelocytes and younger forms are usually not included in this calculation (calculator 1). The risk of infection begins to increase as the ANC declines below 1000/microL (table 1).

The terms leukopenia and granulocytopenia are sometimes used interchangeably with neutropenia, although they are somewhat different. Leukopenia refers to a low total WBC, while granulocytopenia refers to a reduced number of all granulocytes (neutrophils, eosinophils, and basophils). Agranulocytosis literally means the absence of granulocytes, but the term is variably used in the literature to indicate very severe neutropenia (ie, ANC <100/microL, or sometimes even <500/microL).
Fever — Fever in a neutropenic patient is usually defined as a single temperature >38.3°C (101.3°F), or a temperature >38°C (100.4°F) sustained for more than one hour. However, infection can occur in neutropenic patients in the absence of fever. This occurs more often in elderly patients and those receiving corticosteroids. Presenting signs of infection in such patients may include hypothermia, hypotension, confusion, or clinical deterioration. (See "Fever in the neutropenic adult patient with cancer").

MYELOID GROWTH FACTORS (COLONY STIMULATING FACTORS) — CSFs have been evaluated for prophylactic use following the administration of chemotherapy when neutropenia is anticipated ("primary prophylaxis"), during retreatment after a previous cycle of chemotherapy that caused febrile neutropenia ("secondary prophylaxis"), and to shorten the duration of severe chemotherapy-induced neutropenia without fever ("afebrile neutropenia"). The use of CSFs has also been evaluated as an adjunct to other therapies in patients with febrile neutropenia. (See "Fever in the neutropenic adult patient with cancer").

The likelihood of developing febrile neutropenia is the primary factor that determines whether or not prophylactic CSFs are indicated. The incidence of febrile neutropenia following treatment is also influenced by the intensity of chemotherapy, the degree of injury to the gastrointestinal mucosa, the presence of underlying damage to the patient's hematopoietic stem cells, the concurrent use of radiation, and the overall clinical status of the patient (ie, age and comorbid conditions).

Primary prophylaxis — Primary prophylaxis refers to the use of CSFs during the first cycle of myelosuppressive chemotherapy with the goal of preventing neutropenic complications.

Indications and guidelines — Primary prophylaxis may be used to decrease the incidence of febrile neutropenia and the need for hospitalization. Primary prophylaxis may also be used to maintain dose-dense or dose-intense chemotherapy strategies that have survival benefits or if reductions in chemotherapy dose-intensity or dose-density are known to be associated with a poorer prognosis.

We recommend against the routine administration of myeloid CSFs for primary prophylaxis in previously untreated patients receiving chemotherapy regimens with a low probability of causing fever during anticipated periods of neutropenia.

The 2006 guidelines from both the American Society of Clinical Oncology (ASCO) and the European Organization for Research and Treatment of Cancer (EORTC) recommend primary prophylaxis when the anticipated incidence of febrile neutropenia is approximately 20 percent or higher [2,3]. Previous guidelines had recommended a cut-off of 40 percent [4]. The change in recommendation was driven by later randomized trials showing that primary prophylaxis was cost effective when the risk of febrile neutropenia with a specific
regimen exceeded 20 percent [5,6]. This benchmark may change, given the high cost of treatment for febrile neutropenia, which typically involves hospitalization [7].

Evidence from multiple randomized trials supports the benefit of primary prophylaxis in reducing the frequency of hospitalization for antibiotic therapy, documented infection, and rates of febrile neutropenia [6,8-11]. The impact on survival is less clear:

- In a systematic review of the literature and meta-analysis that included 3493 patients treated in 17 randomized controlled trials [11], there was a 46 percent decrease in the risk of febrile neutropenia (relative risk [RR] 0.54, 95% CI 0.43-0.67), as well as a 45 percent decrease in infection-related mortality (RR 0.55, 95% CI 0.33-0.90) and a 40 percent decrease in all-cause mortality during the chemotherapy period (RR 0.60, 95% CI 0.43-0.87). This meta-analysis was not able to address the impact of primary prophylaxis on disease-free and overall survival. The potential benefit of primary prophylaxis in children is less clear [12].
- On the other hand, a meta-analysis of 148 trials of CSF prophylaxis in patients with cancer or undergoing hematopoietic cell transplant also found a significant decrease in the rates of documented infections and febrile neutropenia, but did not confirm a reduction in short-term all-cause mortality or infection-related death [13].

Primary prophylaxis with CSFs may be appropriate in a number of clinical settings in which the estimated risk of febrile neutropenia is less than 20 percent [2,3]:

- Primary prophylaxis may be indicated in patients who are being treated with curative intent (eg, lymphoma, adjuvant treatment for breast cancer, testicular cancer) to reduce the likelihood of dose-limiting neutropenia [14-16]. The benefit of CSFs in this setting was illustrated in a controlled trial in which 80 patients with high-grade non-Hodgkin lymphoma were randomly assigned to receive VAPEC-B chemotherapy alone or with daily G-CSF [14]. The use of G-CSF was associated with less grade 4 neutropenia (37 versus 85 percent), less febrile neutropenia (22 versus 44 percent), and a lesser likelihood of chemotherapy dose reduction (10 versus 33 percent).
- High-risk patients who are treated with less myelosuppressive regimens may also benefit from prophylactic CSFs. This includes the elderly [17], those with preexisting neutropenia, more advanced cancer, poor performance status, or in the case of epithelial ovarian cancer, extensive prechemotherapy surgery, particularly if it included a bowel resection [18]. (See "First-line chemotherapy for epithelial ovarian cancer" and "Epithelial ovarian cancer: Initial surgical management".)
- For patients receiving radiation therapy involving large fields but not chemotherapy, therapeutic use of CSFs may be considered if prolonged delays secondary to neutropenia are expected.
Concomitant chemotherapy and radiation — In some solid tumors, chemotherapy is given concurrently with radiation therapy in an effort to increase local control and survival [19,20]. Combined modality treatment also increases the incidence of febrile neutropenia, compared to radiotherapy alone [19,20].

However, GM-CSF has been associated with a higher incidence of thrombocytopenia and other complications when given with concurrent chemoradiotherapy. This was illustrated in a Southwest Oncology Group trial in which 215 patients with small cell lung cancer were randomly assigned to receive concurrent chemotherapy and thoracic radiotherapy with or without GM-CSF [21]. The incidence of grade 3 and 4 thrombocytopenia was significantly higher in the GM-CSF arm (91 versus 18 percent), and there were more treatment-related deaths among those receiving GM-CSF (9 versus 1, respectively).

This increase in toxicity may be specific to thoracic chemoradiotherapy and/or GM-CSF. Many clinicians avoid CSFs in patients receiving concurrent chemoradiotherapy for lung cancer outside a clinical trial setting.

Acute myeloid leukemia — It is important to bear in mind that malignant myeloblasts typically express receptors for myeloid growth factors. The potential role of CSFs during induction therapy for acute myeloid leukemia is discussed elsewhere. (See "Induction therapy for acute myeloid leukemia in younger adults" and "Treatment of acute myeloid leukemia in older adults".)

Secondary prophylaxis — Secondary prophylaxis refers to the administration of a CSF in subsequent cycles after a neutropenic fever has occurred in a prior cycle. A prior episode of fever during neutropenia is a risk factor for developing fever during neutropenia in further cycles, with recurrences noted in 50 to 60 percent of patients [10,22,23]. Secondary prophylaxis with CSFs reduces this risk by one-half [8].

Secondary prophylaxis also includes the use of a CSF to speed recovery from neutropenia due to a previous cycle of chemotherapy, thus preventing delay in the administration of a subsequent chemotherapy cycle. There are no data proving the benefit of CSFs in this setting. Furthermore, at least some data support the safety of administering adjuvant anthracycline-containing chemotherapy without CSF support or dose reduction in women with uncomplicated neutropenia whose neutrophil count on the day of planned treatment is ≤1500 per microL [24].

In both of these settings, the goal of secondary prophylaxis is to maintain chemotherapy dose intensity while avoiding dose reduction. However, dose reduction after an episode of severe neutropenia should be considered the primary therapeutic option, unless chemotherapy is being administered for the treatment of curable tumors (eg, germ cell cancer, early stage breast cancer) [4]. In theory, the survival benefit associated with
potentially curative chemotherapy should be preserved as long as doses are not reduced below a critical level. However, no published regimen has ever shown improved disease-free or overall survival when secondary prophylaxis was instituted and the dose of chemotherapy maintained in any setting.

ASCO guidelines suggest that secondary prophylaxis with CSFs be limited to patients who experience a neutropenic complication (ie, fever) from a prior cycle of chemotherapy (for which primary prophylaxis was not received) if a reduced dose might compromise treatment outcome [2]. We agree with these recommendations.

Afebrile neutropenia — There is no established role for the use of CSFs in afebrile patients who have already developed severe neutropenia after chemotherapy. This was illustrated in a controlled trial in which 138 afebrile outpatients with severe chemotherapy-induced neutropenia (ANC $\leq 500/\text{microL}$) were randomly assigned to G-CSF or placebo until the ANC recovered to at least 500/\text{microL} [25]. The duration of severe neutropenia was modestly shorter with G-CSF (two versus four days), but there was no effect on the rate of hospitalization or number of culture-positive infections.

Dosage of G-CSF and GM-CSF — The recommended dose for G-CSF is 5 mcg/kg per day and for GM-CSF is 250 mcg/m2 per day, except when these agents are used for the mobilization of peripheral blood progenitor cells. To reduce cost, the dose is usually rounded off to the nearest vial size. Therapy is usually begun 24 to 72 hours after cessation of chemotherapy and is often continued until the absolute neutrophil count reaches 5000 to 10,000/\text{microL}; continuation until clinically adequate neutrophil recovery is achieved is a reasonable alternative [4]. (See "Sources of hematopoietic stem cells" and "Use of recombinant hematopoietic growth factors in stem cell and progenitor cell mobilization".)

Shorter administration schedules may have similar efficacy with lower cost and increased convenience for the patient [26]. However, these approaches have not been compared to standard regimens in randomized trials.

Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, growth factors should be discontinued several days before the next chemotherapy treatment and they should not be given on the same day as chemotherapy [27]. For the same reason, growth factors should not be given concurrently with radiation therapy directed at portals containing active marrow.

Pegfilgrastim — Pegfilgrastim, a pegylated formulation of G-CSF, has a prolonged half-life, permitting the administration of a single dose rather than daily administration. The recommended dose (6 mg in adults, 100 microg/kg, maximum 6 mg in children [28]) is given 24 hours after chemotherapy, with at least 14 days elapsing until the next planned chemotherapy dose.
Multiple randomized trials have shown that pegfilgrastim is as effective as and more convenient to administer than G-CSF for primary prophylaxis in patients requiring CSF treatment during myelosuppressive chemotherapy [29-32]. In the largest of these trials, 310 women with high-risk breast cancer receiving four courses of adjuvant docetaxel and doxorubicin every three weeks were assigned randomly to a single fixed dose of pegfilgrastim (100 mcg/kg) on day 2 of each cycle, or G-CSF (5 mcg/kg per day for 14 days or until the ANC was ≥10,000/microL) [30]. The severity and duration of neutropenia and the side effect profile were similar in both groups.

GM-CSF versus G-CSF — Although many placebo-controlled trials have demonstrated that both G-CSF and GM-CSF are effective at reducing febrile neutropenia and infectious complications in cancer patients receiving chemotherapy, there are only limited comparative data, which are conflicting:

- Only one randomized trial directly compared G-CSF and GM-CSF in 181 afebrile cancer patients undergoing myelosuppressive chemotherapy [33]. Patients receiving G-CSF had a one-day shorter time to recovery from neutropenia, but the difference was neither clinically meaningful nor statistically significant.
- A prospective medication use evaluation study found that G-CSF and GM-CSF have similar efficacy, safety and tolerability [34].
- Two retrospective studies reported that adverse events and/or febrile neutropenia occurred more frequently with GM-CSF than with G-CSF [35,36]. In contrast, a retrospective matched pair cohort analysis derived from a health insurance claims database (and partially funded by the manufacturer of GM-CSF) concluded that patients receiving GM-CSF after outpatient chemotherapy had a lower risk of infection-related hospitalization compared to those receiving G-CSF or pegfilgrastim [37].

In the absence of additional comparative data from randomized controlled trials, there is no basis for recommending one CSF over the other for prophylaxis of infection during chemotherapy-induced neutropenia.

Risk of therapy-related myeloid leukemia — In order to deliver "dose-dense" chemotherapy regimens safely, G-CSF may need to be given during the short intervals between treatment courses. However, such an intensive schedule may increase the likelihood for the survival and proliferation of a hematopoietic stem cell that may have sustained a critical mutation from the previous chemotherapy course and would otherwise have undergone apoptosis or DNA repair.

Several observational studies reported that the use of CSFs is associated with an increased risk of therapy-related acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). However, at least in the setting of adjuvant chemotherapy for breast cancer, a
randomized trial comparing dose-dense therapy (requiring G-CSF support) versus standard-dose chemotherapy failed to demonstrate any increase in secondary MDS/AML in the dose-dense arm. Furthermore, even if there were a small increase in the risk of secondary leukemogenesis, the absolute risk is low (less than 1 percent), and the benefits of using the drug, particularly in the adjuvant setting, likely outweigh the risks. (See "Side effects of adjuvant chemotherapy for early stage breast cancer", section on 'Leukemia and myelodysplastic syndromes' and "Introduction to recombinant hematopoietic growth factors", section on 'Possible stimulation of malignancy'.)

ANTIBACTERIAL AND ANTIFUNGAL PROPHYLAXIS

Antibacterial drugs — Many investigators have sought to determine if the administration of prophylactic antibiotics has a beneficial effect on clinical outcomes. Results have been mixed with respect to effectiveness and have prompted concern about side effects and antimicrobial resistance [38].

A meta-analysis was performed of 95 randomized trials in afebrile neutropenic patients (most of whom had hematologic cancers) comparing antibiotic prophylaxis with placebo with the following results [39]:

- Antibiotic prophylaxis significantly decreased the risk for death when compared with placebo or no treatment (relative risk 0.67, 95% CI 0.55 to 0.81).
- Fluoroquinolone prophylaxis reduced the risk for all-cause mortality (relative risk 0.52, 95% CI 0.35 to 0.77), as well as infection-related mortality, fever, clinically documented infections, and microbiologically documented infections.
- Fluoroquinolone prophylaxis increased the risk for colonization with resistant bacteria, but the difference was not statistically significant.
- All prophylactic antibiotics were associated with an increased risk for adverse events.

Subsequent to this meta-analysis, two additional large, randomized, double-blind placebo-controlled trials of prophylactic fluoroquinolones in patients undergoing cancer chemotherapy were reported [40,41]. Both trials consisted primarily of patients with solid tumors or hematologic malignancies who were at high risk for severe and prolonged neutropenia. The first trial evaluated a higher-risk patient population, mainly inpatients, who received levofloxacin from the time of initiation of chemotherapy until neutrophil recovery [40]. The second trial was in the outpatient setting, and levofloxacin was administered for the seven days estimated to coincide with the neutrophil nadir [41]. The primary endpoint for both trials was the occurrence of fever.

These studies demonstrated the following results:
Prophylactic antibiotics led to a significant decrease in febrile episodes. The inpatient trial failed to document a survival benefit associated with antibiotic prophylaxis [40]. However, the absolute number of deaths was small (10 deaths among 373 treated patients and 18 among 363 in the placebo group), potentially obscuring an impact of antibiotic prophylaxis on survival.

Survival was not a primary or secondary outcome in the outpatient trial; four infection-related deaths were reported in each group [41].

- In the inpatient study, the levofloxacin-treated group had a lower rate of Escherichia coli bacteremia than did the placebo group (1.2 percent versus 3.0 percent). However, prophylaxis was associated with significantly higher rates of antimicrobial resistance (77 percent versus 17 percent). This finding has been noted by others [42].

On the other hand, a subsequent meta-analysis of trials that reported resistance data found that patients who received fluoroquinolones did not develop more infections with bacteria resistant to the drug class than did those receiving placebo [43].

The Infectious Diseases Society of America (IDSA) does not endorse routine antibiotic prophylaxis for neutropenic patients, largely because of the lack of survival advantage, and risk for antibiotic resistance, although the most recent guidelines were published prior to the above studies [44]. In general, we agree with the IDSA guidelines, and we do not routinely recommend fluoroquinolone antibiotic prophylaxis for patients receiving myelosuppressive chemotherapy.

However, there are selected situations in which the increased risk of infection due to the underlying disease or the nature/intensity of the chemotherapy may justify the use of antibiotic prophylaxis [45]. Examples include acute leukemia treated with intensive chemotherapy, chronic lymphocytic leukemia treated with certain drugs (eg, alemtuzumab, pentostatin), multiple myeloma treated with myelosuppressive chemotherapy, locally advanced head and neck cancer treated with sequential therapy with induction chemotherapy followed by radiotherapy, and hematopoietic cell transplantation. (See "Overview of the complications of chronic lymphocytic leukemia" and "Treatment of relapsed or refractory chronic lymphocytic leukemia" and "Initial chemotherapy for symptomatic multiple myeloma in patients who are candidates for transplantation" and "Sequential therapy for locoregionally advanced head and neck cancer" and "Prophylaxis of infections in hematopoietic cell transplant recipients".)

The utility of prophylactic antibiotics in other patient subsets with chemotherapy-induced neutropenia remains controversial. In light of resistance issues, efforts to improve patient
risk stratification will be critical to minimize unnecessary use of antimicrobial agents and to preserve their efficacy [26,46].

Systemic antifungal drugs — Given the rise in the incidence of life-threatening invasive fungal infections among cancer patients over the last two decades [47], there has also been interest in antifungal prophylaxis for patients receiving chemotherapy. A 2007 meta-analysis included 49 randomized trials that compared systemic antifungal prophylaxis versus a control arm (placebo, no intervention, or a nonsystemic antifungal agents [eg, clotrimazole]) in cancer patients receiving myelosuppressive chemotherapy (predominantly for acute leukemia) or undergoing hematopoietic cell transplantation [48]. In patients with acute leukemia, antifungal prophylaxis was associated with significant reductions in documented invasive fungal infections (RR 0.69, 95% CI 0.53-0.90) and fungal-related mortality (RR 0.66, 95% CI 0.44-1.00).

The relative efficacy of different antifungal agents was addressed in a randomized, multicenter trial of 602 patients with prolonged neutropenia due to chemotherapy for acute myeloid leukemia or myelodysplastic syndrome [49]. The patients were assigned to posaconazole or either fluconazole or itraconazole. Prophylaxis was given with each cycle of chemotherapy until recovery from neutropenia and complete remission, occurrence of an invasive fungal infection, or for up to 12 weeks, whichever came first.

**Posaconazole** prophylaxis was associated with a significant reduction in proven or probable invasive fungal infections (2 versus 8 percent) that was entirely due to a reduction in invasive aspergillosis. Posaconazole was also associated with a significant increase in both survival and adverse effects that were mostly gastrointestinal (6 versus 2 percent).

Although these data suggest a benefit from antifungal prophylaxis, issues surrounding overuse of these drugs (eg, resistance, toxicity and cost) and the relatively low incidence of invasive fungal infections in these patients have tempered enthusiasm for universal prophylaxis.

It is important to distinguish between moderate chemotherapy-induced neutropenia expected to be of short duration in otherwise healthy patients and prolonged severe neutropenia associated with diseases such as acute leukemia or following intensive myelosuppressive chemotherapy. The risk:benefit assessment must account for profound immunosuppression (such as occurs during induction chemotherapy for acute leukemia or after allogeneic hematopoietic cell transplantation), comorbidities such as older age, mucositis, poorly controlled diabetes, smoking history, and recurrent use of antibacterial agents, to identify those individuals at increased risk of fungal infection. Major organizations such as the National Comprehensive Cancer Network (NCCN) [50], the United States Centers for Disease Control and Prevention [51], the Infectious Diseases Society of America, the American Society of Blood and Marrow Transplantation, and
<p>Others [52,53] recommend systemic antifungal prophylaxis for high-risk patients. (See "Induction therapy for acute myeloid leukemia in younger adults", section on 'Prophylaxis' and "Engraftment and supportive care after hematopoietic cell transplantation").</p>

Aerosolized liposomal amphotericin B — The efficacy of aerosolized liposomal amphotericin B in preventing invasive pulmonary aspergillosis was evaluated in a randomized, placebo-controlled trial of 271 patients (during 407 neutropenic episodes) with hematological disease who were expected to be neutropenic for at least 10 days [54]. In the intent-to-treat analysis, aerosolized amphotericin B was associated with a significant reduction in the rate of invasive aspergillosis (4.3 versus 13.6 percent with placebo, odds ratio 0.26, 95% CI 0.09-0.72). No survival benefit was observed, but this study was probably underpowered to detect such an effect [55].</p>

Aerosolized amphotericin B has not been directly compared to systemic antifungal prophylaxis. Thus, additional studies are needed before this therapy can be recommended for patients who require antifungal prophylaxis [55].

**SUMMARY AND RECOMMENDATIONS** — The myeloid colony stimulating factors (CSFs) have been widely evaluated to minimize the extent and duration of neutropenia associated with intensive cytotoxic chemotherapy or radiation therapy (RT). Despite their effects on neutropenia, prophylactic use of myeloid CSFs has not been demonstrated to be cost effective or to have an impact on survival in most clinical situations. (See 'Colony stimulating factors' below.)</p>

Antibiotic prophylaxis has been used to prevent the development of documented infections in patients with severe neutropenia. Although the routine use of antibiotic prophylaxis is not recommended, there may be some groups of patients for whom it should be given. (See 'Antibacterial and antifungal prophylaxis' above.)</p>

**Colony stimulating factors**

- **Primary prophylaxis** — In keeping with ASCO guidelines [2], when the incidence of febrile neutropenia is expected to be less than 10 percent following chemotherapy, we recommend that CSFs not be routinely administered for primary prophylaxis (Grade 1A).

When the expected incidence of febrile neutropenia is over 20 percent, we suggest prophylactic CSFs to reduce the need for hospitalization for antibiotic therapy (Grade 2A). CSFs may also be used to maintain dose-dense or dose-intense chemotherapy strategies that have survival benefits or in settings where reductions in chemotherapy dose-intensity or
dose-density are known to be associated with a poorer prognosis. (See 'Primary prophylaxis' above.)

When the estimated risk of febrile neutropenia is between 10 and 20 percent, we suggest that the decision to use hematopoietic growth factor support be individualized. Patients who may be at risk for increased complications from prolonged neutropenia for whom primary prophylaxis might be justified include the following categories [2]:

- Age 65 and older
- Poor performance status
- Prior episodes of febrile neutropenia
- Large radiation portals, or receiving combined chemoradiotherapy
- Cytopenias due to marrow involvement
- Poor nutritional status
- Open wounds or active infection
- Advanced cancer or other serious comorbidities

- Secondary prophylaxis — For patients who had an episode of febrile neutropenia after an earlier cycle of palliative chemotherapy, we suggest that dose reduction or delay be the primary therapeutic option and that CSFs not be administered routinely (Grade 2B). (See 'Secondary prophylaxis' above.)

However, in keeping with ASCO guidelines [2], when the risk of febrile neutropenia would prevent the administration of full doses of potentially curative chemotherapy, we suggest the use of CSFs for secondary prophylaxis rather than dose reduction (Grade 2B). (See 'Primary prophylaxis' above and 'Secondary prophylaxis' above.)

- Afebrile neutropenia — For afebrile patients in whom severe neutropenia has already developed after chemotherapy, we suggest that CSFs not be used (Grade 2B). (See 'Afebrile neutropenia' above.)

Antibacterial and antifungal prophylactic regimens — The recommendations for antibiotic prophylaxis vary with the clinical setting. For most patients with chemotherapy-induced neutropenia expected to be of short duration, we suggest avoiding the routine use of antibiotic prophylaxis (Grade 2A). However, antibiotic prophylaxis against enteric bacteria and fungi may be useful in some patients with hematologic malignancies, in whom prolonged bone marrow suppression or immunosuppression from the underlying disease or type of chemotherapy regimen increases the risk of infections. (See 'Antibacterial and antifungal prophylaxis' above.)

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REFERENCES


27. Skarlos, DV, Timotheadou, E, Galani, E, et al. Pegfilgrastim administered on the same day with dose-dense adjuvant chemotherapy for breast cancer is associated with a higher incidence of febrile neutropenia as compared to conventional growth factor support: matched case-control study of the Hellenic Cooperative Oncology Group. Oncology 2009; 77:107.


50. National Comprehensive Cancer Network (NCCN) guidelines are available online at www.nccn.org.


INTRODUCTION — Fever and neutropenia are common in children with primary hematologic diseases. The risk of developing an infection and the types of pathogens isolated differ depending upon the underlying disorder. The management of children with fever and chronic neutropenic disorders is reviewed here. The definition of neutropenia, conditions that cause neutropenia, the risk of infection in children with neutropenia, and fever in children with chemotherapy-induced neutropenia are discussed separately. (See "Risk of infection in children with non-chemotherapy-induced neutropenia" and "Fever in children with chemotherapy-induced neutropenia".)

GUIDELINES FOR TREATMENT OF FEVER AND NEUTROPENIA — Guidelines for the management of fever and neutropenia in the cancer patient have been derived from controlled clinical trials. Similar validated therapeutic approaches to fever in the patient with other forms of neutropenia have not been developed because of the rarity of the primary neutropenic disorders. Thus, management of the high-risk patient with chronic neutropenia generally is extrapolated from the care of the patient with chemotherapy-induced neutropenia. However, depending on the cause and severity of neutropenia (table 1), the febrile patient with neutropenia not caused by chemotherapy may not have the same risk for viral, fungal, and parasitic infections as the patient receiving long-term or intensive chemotherapy.

Initiation of empiric broad-spectrum antibiotic therapy for fever and neutropenia is required in any ill-appearing patient and for patients with underlying severe aplastic anemia or congenital neutropenia. Patients with chronic neutropenia or cyclic neutropenia who have experienced a life-threatening infection or have recurrent infections should be similarly treated.

DEFINITIONS OF FEVER — Fever in neutropenic patients generally is defined as a single oral temperature >38.3°C (101°F) [1]. A temperature ≥38°C (100.4°F) for longer than one hour or two elevations >38°C during a 12-hour period are definitions of fever that also are used [2,3].
Fever often is the sole sign of occult infection in the neutropenic host. However, this sign may be absent in some infected patients who instead may be hypothermic, hypotensive, listless, or confused. Thus, infection must be considered and treated empirically if any signs of clinical deterioration are present in a neutropenic child, regardless of the recorded temperature.

MEASUREMENT OF TEMPERATURE — Measuring the temperature orally is preferable, although an axillary temperature is acceptable if the patient is unable to use an oral thermometer. Generally, no conversion is made between axillary and oral temperatures. However, more conservative guidelines suggest that adding 0.5ºF (0.3ºC) to the axillary temperature reading may be warranted. Because of associated risks of mucosal trauma and bacteremia, measurement of rectal temperature should be avoided in neutropenic patients.

INITIAL EVALUATION — Because of the substantial risk of a life-threatening infection in the febrile neutropenic child, the initial evaluation must be conducted promptly.

Physical examination — A careful physical examination should be performed, with particular attention paid to those sites most commonly infected, including:

- Skin, especially folds, areas surrounding nail beds, and central venous line sites and subcutaneous tunnel, if present
- Sinuses; sinus tenderness should be evaluated
- Oropharynx, with attention to the gingiva
- Lungs
- Abdomen
- Perineum, particularly the perianal and labial regions

Mild erythema or tenderness should not be ignored because signs of inflammation in the neutropenic patient may be subtle. Repeated physical examinations are essential. Visual signs of inflammation may become evident only when neutrophil counts are recovering.

Cultures — Blood cultures should be obtained without delay. Blood cultures should be taken from the central line when such access is available. Opinions vary as to whether blood should also be cultured from peripheral sites in these patients [4-6]. The rationale for culturing both peripheral and central sites is to differentiate a catheter-related infection from bacteremia from another source. However, peripheral cultures may be positive in patients with significant central catheter-related infections [7]. In addition, treatment recommendations for central catheter-related infections and for bacteremias from other sources are the same in cancer patients [3,7]. Thus, we do not recommend the routine culturing of blood from peripheral sites in addition to central sites, unless contrary institutional practice guidelines are in place.
Obtaining more than one blood culture is helpful in the interpretation of blood culture results. As an example, true bacteremia is more likely when coagulase-negative staphylococci are isolated from two or more blood cultures than from a single culture, which may be reflective of a contaminated specimen. In addition, the practice of sampling all lumens of a multiple-lumen central venous catheter is supported by two studies in which 32 to 43 percent of positive cultures from multiple-lumen catheters were positive from only one lumen [4,8].

The only other site that may be useful to culture routinely is urine in febrile, neutropenic girls. In one study, urinary tract infections accounted for 11 percent of all documented infections in febrile neutropenic patients, and 76 percent of these occurred in girls [9].

Additional studies — Additional studies should be obtained as clinically indicated. Examples include:

- Chest radiographs in children with respiratory signs and symptoms [10]. A chest radiogram that is negative for infiltrates should be interpreted with caution since infiltrates may not appear until neutrophil counts are recovering.
- Abdominal radiographs and/or ultrasound in children with abdominal signs and symptoms, particularly abdominal pain [11]
- Lumbar puncture for altered mental status or meningeal signs
- Stool culture, Clostridium difficile toxin, ova, parasites, and viral cultures in patients with diarrhea
- Culture and Gram stain of drainage from any site with drainage

EMPIRIC ANTIBIOTICS — The cornerstone of treatment for the febrile, neutropenic patient at high risk for infection is prompt initiation of empiric broad-spectrum antibiotic therapy. Specific sites of infection, if present, will guide the choice of antibiotics. When choosing empiric therapy, the practitioner should consider:

- The types of bacterial isolates found in the institution
- Antibiotic susceptibility patterns
- The patient's drug allergies (if any)
- Presence of organ dysfunction, particularly renal and hepatic
- History and cause of previous life-threatening infections
- Whether the patient was receiving prophylactic antimicrobials

Suggested regimens — Care for the high-risk hematology patient is extrapolated from the care of the cancer patient with chemotherapy-induced neutopenia. Both groups of patients are at risk for infections caused by gram-positive and gram-negative organisms, and thus, empiric antibiotic therapy should be effective against a broad spectrum of potential pathogens. Although gram-positive organisms represent the majority of isolates in febrile
neutropenia patients, empiric antibiotic therapy should ensure adequate (and preferably synergistic) gram-negative coverage because of the potential for a life-threatening infection with gram-negative organisms.

Many studies have demonstrated that monotherapy with a broad-spectrum antipseudomonal agent (such as ceftazidime) or a carbapenem (such as imipenem-cilastin) is as efficacious as combination therapy for the empiric treatment of most febrile neutropenic patients [12-14]. Monotherapy is considered standard therapy for uncomplicated episodes of fever [3,15]. Acceptable monotherapy regimens include:

- **Cefepime**: 50 mg/kg (to a maximum of 2 g per dose) administered IV every eight hours. (See "Cefepime: Drug information", or
- **Ceftazidime**: 50 mg/kg (to a maximum of 2 g per dose) administered IV every eight hours; the dosing interval should be adjusted for renal dysfunction. (See "Ceftazidime: Drug information", or
- **Imipenem-cilastatin**: 25 mg/kg (to a maximum of 1 g per dose) administered IV every six hours for infants older than one month and children; the dose and dosing interval should be adjusted for renal dysfunction. (See "Imipenem and cilastatin: Drug information").

The alternative to monotherapy is combination therapy with an aminoglycoside (eg, gentamicin) plus an antipseudomonal agent (eg, ticarcillin-clavulanate), cefepime, ceftazidime, or a carbapenem [3]. Combination therapy has potential advantages for the patient at high risk for bacterial infection. These include synergistic effects against some gram-negative and gram-positive organisms and possible reduction in the emergence of resistant organisms during treatment. The major disadvantage of combination therapy is the toxicity, particularly nephrotoxicity, of aminoglycosides.

A sample combination therapy regimen is gentamicin plus ticarcillin-clavulanate as follows:

- **Gentamicin** — 2.5 mg/kg per dose (for patients <50 kg) or 1.5 to 2.0 mg/kg per dose, to a maximum of 120 mg per dose (for patients >50 kg) administered IV every eight hours; the dose and dosing interval should be adjusted according to serum concentrations for renal dysfunction. (See "Gentamicin: Patient drug information").
- **Ticarcillin-clavulanate** — 75 mg/kg per dose (to a maximum of 3.1 g per dose) administered IV every six hours; the dose should be adjusted for renal dysfunction. (See "Ticarcillin and clavulanate potassium: Drug information").

If abdominal symptoms are present, particularly abdominal pain or blood per rectum, metronidazole should be added to broaden coverage for anaerobes [16].
In selective cases, empiric antibiotic therapy could be transferred to an ambulatory setting after an initial period of 48 hours, when blood culture negativity is insured. Outpatient therapy could have substantial financial implications, in addition to its impact on ancillary resources [17].

Modifications — Regardless of the initial empiric choice, modification of the regimen must be considered in the following circumstances:

- Change in clinical status or vital signs
- Persistent fever for >48 hours
- Isolation of an organism from the blood
- Development of signs or symptoms of a localized infection

For those patients in whom a site of infection has been defined and who are afebrile, therapy can be adjusted to the most appropriate treatment for the particular infection [3].

Vancomycin — **Vancomycin** is a logical drug to include in a broad-spectrum regimen to improve coverage of gram-positive organisms, but the necessity of doing so has not been proven. One-half or more of bacterial isolates in febrile neutropenic cancer patients are gram-positive cocci, and frequently coagulase-negative staphylococci resistant to extended-spectrum penicillins or third-generation cephalosporins. However, antibiotic regimens without vancomycin have not been associated with increased risk of morbidity or mortality [18-20]. This observation probably also holds true for the febrile neutropenic hematology patient. A history of, or increased risk for, infections with alpha-hemolytic streptococci may be an exception [20].

The administration of vancomycin increases the possibility of colonization or infection with vancomycin-resistant enterococci (VRE). Efforts to decrease the emergence of VRE and the possible spread of vancomycin resistance to other gram-positive organisms, such as Staphylococcus aureus, strongly discourage the empiric use of vancomycin in patients with fever and neutropenia.

The Hospital Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention (CDC) has recommended guidelines for the use of vancomycin that have been implemented by many institutions [21]. These guidelines include using vancomycin in febrile neutropenic patients only when there is a strong suspicion of infection with a gram-positive organism.

Indications — Extrapolating from the 2002 guidelines of the Infectious Diseases Society of America (IDSA) for febrile neutropenia in cancer patients, vancomycin is recommended for febrile neutropenia in hematology patients for the following clinical scenarios [3]:
• Clinically suspected central venous line site infection
• Known colonization with methicillin-resistant S. aureus (MRSA), or penicillin- and cephalosporin-resistant Streptococcus pneumoniae. (See "Treatment of invasive methicillin-resistant Staphylococcus aureus infection in children").
• When a blood culture is reported to be growing gram-positive bacteria, and identification and sensitivity testing are pending
• Hypotension or other signs of cardiopulmonary deterioration

Additional indications for vancomycin may include:

• Prior use of quinolone prophylaxis during afebrile neutropenia
• Previous history of infection with penicillin-resistant streptococci

Consideration should be given to the inclusion of vancomycin in the initial empiric antibiotic regimen in institutions with a high rate of bacteremia caused by penicillin-resistant alpha-hemolytic streptococci [20].

The full text of the IDSA guideline is available separately and can be accessed through the Infectious Diseases Society of America's Web site [22].

Substantial efforts have been focused on modifying the dose schedule of aminoglycosides to achieve a better toxicity profile, such as using single daily dosing or their elimination altogether from empiric (and potentially prolonged) antibiotic regimens [17,23,24]. Although such efforts are promising, larger studies are warranted prior to changing the currently available guidelines.

Antifungal therapy — Patients with persistent fever and neutropenia despite empiric antibacterial therapy could have a clinically occult fungal infection. This is a particularly important consideration for patients with severe aplastic anemia, for whom invasive fungal infections are a major cause of death [25].

Amphotericin B is active against a broad spectrum of fungi, including Aspergillus and Candida sps. It should be administered to patients who have remained febrile and profoundly neutropenic after five to seven days of broad-spectrum antibiotics [2].

A sample amphotericin B dosing schedule is:

• 0.5 mg/kg per dose administered IV once daily for empiric therapy; 1.0 to 1.5 mg/kg per dose administered IV once daily for documented fungal infections.

Despite the potential benefits of empiric amphotericin B therapy, the substantial toxicity, particularly nephrotoxicity, which may accompany its administration, limits its use in many
patients. Less toxic alternatives, including lipid formulations of amphotericin B and voriconazole, are being studied in cancer patients, with promising results. These studies and their results are discussed separately. (See "Fever in children with chemotherapy-induced neutropenia", section on 'Antifungal therapy'.)

Whether similar results would be observed in a population of exclusively neutropenic hematology patients is unclear, particularly among patients with severe aplastic anemia, in whom Aspergillus sp. are frequent pathogens as compared with cancer patients in whom Candida sp. predominate. (See "Risk of infection in children with non-chemotherapy-induced neutropenia").

In a multicenter randomized trial, the tolerability, efficacy, and safety of caspofungin were comparable to those of liposomal amphotericin B for empiric antifungal therapy in pediatric patients with persistent fever and neutropenia [26].

Fluconazole is not active against Aspergillus species. It is therefore a poor choice for empiric antifungal therapy for the patient with neutropenia and prolonged fever.

Duration of therapy — Unlike patients with cytotoxic therapy-induced neutropenia, the duration of neutropenia in the patient with aplastic anemia and other forms of stable chronic neutropenia is indeterminate, complicating the decision about the duration of empiric therapy when no source of infection is identified. Results of a sentinel study of infection in patients with aplastic anemia suggest that empiric antibiotic therapy should continue for 10 to 14 days, followed by careful observation [27].

GRANULOCYTE-COLONY STIMULATING FACTOR (G-CSF) — The benefits of initiating granulocyte-colony stimulating factor (G-CSF, filgrastim, lenograstim) in neutropenic hematology patients with established fever remain anecdotal. However, there are data on the use of G-CSF to increase neutrophil counts and reduce episodes of fever and infection in patients with various types of chronic neutropenia, as illustrated below:

- A randomized trial in patients with idiopathic chronic neutropenia, cyclic neutropenia, and congenital neutropenia demonstrated that G-CSF increased neutrophil counts and reduced episodes of fever, infection, and hospitalization [28]. Virtually all of the patients with idiopathic chronic neutropenia and cyclic neutropenia responded, whereas only 83 percent of those with congenital neutropenia did. In addition, higher doses of G-CSF were required to achieve a response in patients with congenital neutropenia than in those with idiopathic chronic neutropenia or cyclic neutropenia (up to 15 mcg/kg per day versus 1 to 5 mcg/kg per day).
- A report on 853 patients from the Severe Chronic Neutropenia International Registry included 429 children with idiopathic, cyclic, and congenital neutropenia,
almost all of whom were treated with G-CSF [29]. Ninety-two percent of all treated patients (including adults) responded to G-CSF at doses <30 mcg/kg per day with an increase in mean neutrophils to >1500/microL.

The use of G-CSF in the treatment of each of these disorders is discussed in detail separately. (See "Primary immune neutropenia", section on 'Chronic idiopathic neutropenia' and "Cyclic neutropenia", section on 'Treatment' and "Congenital neutropenia", section on 'Severe congenital neutropenia'.)

For those children not routinely receiving G-CSF, interventional G-CSF may be appropriate for complicated febrile episodes requiring hospitalization. Such children should be treated in specialized centers by clinicians with expertise in the use of G-CSF. (See "Introduction to recombinant hematopoietic growth factors" and "Recombinant hematopoietic growth factors in inherited bone marrow failure syndromes".)

SUMMARY AND RECOMMENDATIONS

- Fever and neutropenia are common in children with primary hematologic diseases. The risk of developing an infection and the types of pathogens isolated differ depending upon the underlying disorder (table 1).
- The approach to fever in the child with non-chemotherapy-induced neutropenia typically parallels that for the children with chemotherapy-induced neutropenia. (See "Fever in children with chemotherapy-induced neutropenia").
- Fever in the neutropenic patient may be defined as a single oral temperature >38.3ºC (101ºF), a temperature ≥38ºC (100.4ºF) for longer than one hour, or two elevations >38ºC during a 12-hour period. (See 'Definitions of fever' above.)
- Measuring the temperature orally is preferable; an axillary temperature is an acceptable alternative and is considered to be equivalent to an oral temperature without conversion. However, more conservative guidelines suggest that adding 0.5 degrees to the axillary temperature reading may be warranted. Measurement of rectal temperatures should be avoided in neutropenic patients. (See 'Measurement of temperature' above.)
- The initial evaluation must be conducted promptly because of the substantial risk of a life-threatening infection. Serial examination of the most common sites of infection is essential. (See 'Physical examination' above.)
- Blood cultures should be obtained without delay. Cultures should be obtained from the central line if one is present. We suggest obtaining cultures from all lumens if the central line has multiple lumens. We suggest not obtaining peripheral blood cultures in addition to central line cultures in patients with central lines. (See 'Cultures' above.)
We suggest that urine culture be obtained in febrile girls with neutropenia. Additional studies should be obtained as clinically indicated. (See 'Cultures' above and 'Additional studies' above.)

We recommend prompt initiation of empiric broad-spectrum antibiotic therapy that ensures both gram-negative and gram-positive coverage (Grade 1A). The choice of antibiotic is guided by the site of infection if a specific infection is present. (See 'Suggested regimens' above.)

- We suggest monotherapy with cefepime, ceftazidime, or imipenem-cilastin for uncomplicated episodes of fever (Grade 2B).
- We suggest combination therapy with an aminoglycoside and an antipseudomonal agent for the patient at high risk for bacterial infection (table 1) (Grade 2B).
- We suggest the addition of metronidazole for the patient with abdominal symptoms (Grade 2C).

The use of vancomycin should be reserved for febrile neutropenic patients with certain well-defined clinical scenarios. (See 'Vancomycin' above.)

The initial empiric regimen should be modified if there is a change in clinical status or vital signs, fever persists for >72 hours, an organism is isolated from the blood, or the patient develops signs or symptoms of a localized infection. In addition, for those patients in whom a site of infection has been defined and in whom fever has resolved, therapy can be adjusted to the most appropriate treatment for the particular infection. (See 'Modifications' above.)

We suggest that antifungal therapy be administered to patients who remain febrile and profoundly neutropenic after five to seven days of broad-spectrum antibiotics (Grade 2C). (See 'Antifungal therapy' above.)

Empiric antibiotic therapy is usually continued for 10 to 14 days, followed by careful observation. (See 'Duration of therapy' above.)

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REFERENCES


