Overview of neutropenic fever syndromes

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INTRODUCTION

Cancer patients receiving cytotoxic antineoplastic therapy sufficient to adversely affect myelopoiesis and the developmental integrity of the gastrointestinal mucosa are at risk for invasive infection due to colonizing bacteria and/or fungi that translocate across intestinal mucosal surfaces. Since the magnitude of the neutrophil-mediated component of the inflammatory response may be muted in neutropenic patients [1], a fever may be the earliest and only sign of infection. It is critical to recognize neutropenic fever early and to initiate empiric systemic antibacterial therapy promptly in order to avoid progression to a sepsis syndrome and possibly death.

Guidelines have been developed for the evaluation and management of fever in neutropenic patients with cancer [2-4]. The recommendations below are generally in keeping with the 2010 Infectious Diseases Society of America (IDSA) guidelines and the 2018 American Society of Clinical Oncology (ASCO)/IDSA guidelines [2,4]. (See 'Society guideline links' below.)

This topic will provide an overview of the concepts related to neutropenic fever, including definitions of fever and neutropenia and categories of risk. The risk assessment and diagnostic approach to patients presenting with neutropenic fever are discussed in detail separately. The management of neutropenic fever syndromes in cancer patients at high and low risk for complications and the prophylaxis of infections in such patients are also discussed in detail separately. Granulocyte transfusions are also reviewed elsewhere. (See "Risk assessment of adults with chemotherapy-induced neutropenia" and "Diagnostic approach to the adult cancer patient with neutropenic fever" and "Treatment of neutropenic fever syndromes in adults with hematologic malignancies and hematopoietic cell transplant recipients (high-risk patients)" and "Treatment and prevention of neutropenic fever syndromes in adult cancer patients at low risk for complications" and "Prophylaxis of infection during chemotherapy-induced neutropenia in high-risk adults" and "Prophylaxis of invasive fungal infections in adults with hematologic malignancies" and "Prophylaxis of invasive fungal infections in adult hematopoietic cell transplant recipients" and "Use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation" and "Granulocyte transfusions".)

DEFINITIONS

Fever — The definition of fever as an indicator of infection in neutropenic patients has varied. In 1868, Carl Wunderlich proposed that the mean normal body temperature was 37°C (98.6°F) with an upper limit of normal of 38°C (100.4°F), above which fever was defined [5-7]. Despite the observation that there is a range of normal body temperatures, in one survey, a majority (75 percent) of 270 medical professionals reported the belief that normal body temperature is 37°C (98.6°F) [7,8]. A survey of members of the British Society for Haematology regarding their institutional definitions of fever identified 10 definitions of fever, ranging from a single temperature >37.5°C to either a single temperature >39°C or two successive temperatures >38.4°C [9]. These beliefs notwithstanding, the empirically observed mean oral temperature of 148 healthy adults between the ages 18 and 40 years was reported as 36.8±0.4°C (98.2±0.7°F) with a range of 35.6°C (96.0°F) to 38.2°C (100.8°F), the latter defining the upper limit of normal [6].

The Infectious Diseases Society of America defines fever in neutropenic patients as a single oral temperature of ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) sustained over a one-hour period [2]. We agree with using this definition of fever in neutropenic patients. Similar definitions have been provided from South America, Europe, and Asia [10-12].

It is known from animal models that glucocorticoids may have a mitigating effect on the development of fever due to bacterial or endogenous pyrogens [13]. The antipyretic effect of concomitant use of glucocorticoids in neutropenic patients may confound the recognition of an infection [14]. The presence of signs of systemic inflammatory response syndrome (SIRS), including tachycardia, tachypnea, or hypotension in an afebrile neutropenic patient who is receiving concomitant glucocorticoids, should raise the suspicion of infection.

Neutropenia — The definition of neutropenia may vary from institution to institution, but neutropenia is usually defined as an absolute neutrophil count (ANC) <1500 or 1000 cells/microL, severe neutropenia as an ANC <500 cells/microL or an ANC that is expected to decrease to <500 cells/microL over the next 48 hours, and profound neutropenia as an ANC <100 cells/microL [2,15]. The risk of clinically important infection rises as the neutrophil count falls below 500 cells/microL and is higher in those with a prolonged duration of neutropenia (>7 days). Further, the risk for bacteremic infection increases as the ANC decreases below 100 cells/microL. For the purposes of this discussion, **we are defining severe neutropenia as an ANC <500 cells/microL (<0.5 x 10^9/L).**

The ANC can be calculated by multiplying the total white blood cell (WBC) count by the percentage of polymorphonuclear cells (PMNs) and band neutrophils (calculator 1). (See "Overview of neutropenia in children and adolescents", section on 'Definitions and normal values' and "Approach to the adult with unexplained neutropenia", section on 'Definitions and normal values'.)

Assessment of the risk of neutropenia before the WBC and differential results are available is discussed separately. (See "Treatment of neutropenic fever syndromes in adults with hematologic malignancies and hematopoietic cell transplant recipients (high-risk patients)", section on 'Risk of neutropenia'.)

Neutropenic fever syndromes — A number of neutropenic fever syndromes have been described [16,17]. The International Immunocompromised Host Society has classified initial neutropenic fever syndromes into the following three categories [16]:

- Microbiologically documented infection – Neutropenic fever with a clinical focus of infection and an associated pathogen
- Clinically documented infection – Neutropenic fever with a clinical focus (eg, cellulitis, pneumonia) but without the isolation of an associated pathogen
- Unexplained fever – Neutropenic fever with neither a clinical focus of infection nor an identified pathogen

The first neutropenic fever is the first febrile episode occurring during a given period of chemotherapy-induced neutropenia. A persistent neutropenic fever syndrome is a febrile episode without defervescence after at least five days of initial empiric broad-spectrum antibacterial therapy in high-risk neutropenic patients or after at least two days in low-risk neutropenic patients. A recrudescent neutropenic fever syndrome is a febrile episode that recurs following initial defervescence during a course of broad-spectrum antibacterial therapy. (See 'Risk of serious complications' below.)

The **myeloid reconstitution syndrome** is defined by fever and a new inflammatory focus or progression of a preexisting inflammatory focus in temporal relationship to neutrophil recovery from aplasia. This syndrome is similar to the immune reconstitution inflammatory syndrome that can follow the initiation of antiretroviral therapy in patients with HIV infection. (See "Immune reconstitution inflammatory syndrome".)

RISK OF SERIOUS COMPLICATIONS

The initial clinical evaluation focuses on assessing the risk for serious complications. This risk assessment dictates the approach to therapy, including the need for inpatient admission, intravenous antibiotics, and prolonged hospitalization (table 1).

Validated scoring systems used to estimate the risk for medical complications include the Talcott rules [18], the Multinational Association for Supportive Care in Cancer (MASCC) score (calculator 2) [19], and the Clinical Index of Stable Febrile Neutropenia (CISNE) score [20]. These scoring systems assume the states of neutropenia and fever for a given patient and do not focus upon either the degree or duration of neutropenia as predictors of the likelihood of medical complications that require or prolong hospitalization. Only the CISNE score considers the absolute monocyte count in the estimate of complication risk. Further, the CISNE score predicts three levels of risk of serious complications: low (score = 0), intermediate (score = 1 to 2), and high (score ≥3). These scoring systems, while imperfect, may help to inform the clinician's decision regarding the conditions (eg, inpatient versus outpatient, parenteral versus oral) under which initial empiric antibacterial therapy is administered.

- Low-risk patients are those who are expected to be severely neutropenic (absolute neutrophil count [ANC] <500 cells/microL) for ≤7 days, have an MASCC score ≥21 or a CISNE score of 0 at the time of assessment, and who have no comorbidities or evidence of significant hepatic or renal dysfunction. This group of patients has been well studied in randomized trials and has been shown to be at low risk for serious complications [2]. Most patients receiving chemotherapy for solid tumors are considered to be low risk for complications requiring hospitalization or prolonging hospitalization.
- High-risk patients are those who are expected to be severely neutropenic (ANC <500 cells/microL) for >7 days and who have an MASCC score <21 or a CISNE score of ≥3 at the time of assessment. Intermediate CISNE scores (1 or 2) may require clinicians to judge the relative safety of outpatient oral therapy versus hospitalization for parenteral antibacterial therapy. Patients with neutropenic fever who have ongoing comorbidities or evidence of significant hepatic or renal dysfunction are also considered to be high risk for medical complications, regardless of the duration of neutropenia. Other criteria that confer a high-risk status can be found in the table (table 1). Based upon MASCC scores of ≥21, 15 to 20, and <15, the observed risks for serious complications and death have been 8 and 2 percent, 23 and 9 percent, and 37 and 29 percent, respectively [21].

  Some experts have defined high-risk patients as those expected to have profound neutropenia (ANC ≤100 cells/microL) for >7 days based on experience that such patients are the most likely to have life-threatening complications [2,3]. However, formal studies to clearly differentiate between patients with an ANC <500 cells/microL and ≤100 cells/microL are lacking. For the purposes of this discourse, we will combine these groups [4]. Profound prolonged neutropenia (ie, ANC ≤100 cells/microL expected to last >7 days) is most likely to occur in the pre-engraftment phase of hematopoietic cell transplantation (particularly allogeneic) and in patients undergoing induction chemotherapy for acute leukemia.

The risk assessment of patients with neutropenic fever is discussed in greater detail separately. (See "Risk assessment of adults with chemotherapy-induced neutropenia".)

In general, neutropenic fevers develop in approximately 5 to 10 percent of solid tumor patients receiving cytotoxic therapy and who are at low risk for medical complications [22], compared with 20 to 25 percent of non-leukemic hematologic malignancy patients and 85 to 95 percent of acute leukemia patients (table 2) [23].

APPROACHES TO MANAGEMENT

Approaches to the management of infection in patients at risk for neutropenic fever include primary prophylaxis, secondary prophylaxis, empiric therapy, and preemptive therapy.

Primary prophylaxis — Primary prophylaxis involves the administration of an antimicrobial drug to prevent infection in patients at increased risk. (See "Prophylaxis of infection during chemotherapy-induced neutropenia in high-risk adults" and "Treatment and prevention of neutropenic fever syndromes in adult cancer patients at low risk for complications", section on 'Prevention' and "Prophylaxis of invasive fungal infections in adults with hematologic malignancies" and "Prophylaxis of invasive fungal infections in adult hematopoietic cell transplant recipients".)

Secondary prophylaxis — Secondary prophylaxis involves the administration of prophylactic doses of an antimicrobial drug to prevent recurrent infection. (See "Prophylaxis of invasive fungal infections in adults with hematologic malignancies", section on 'Secondary prophylaxis'.)

Empiric therapy — In patients with chemotherapy-induced neutropenia, empiric therapy involves the initiation of therapy at the time of the onset of neutropenic fever but before a firm diagnosis of infection has been established. Empiric antimicrobial therapy is a standard part of the management of neutropenic fever. (See "Treatment of neutropenic fever syndromes in adults with hematologic malignancies and hematopoietic cell transplant recipients (high-risk patients)" and "Treatment and prevention of neutropenic fever syndromes in adult cancer patients at low risk for complications".)

Preemptive therapy — Preemptive therapy involves the initiation of therapy based upon screening with a sensitive microbiology assay (eg, antigen detection or molecular assays) in an attempt to detect the presence of a putative pathogen or early subclinical infection. Patients whose infections are detected using a preemptive approach are treated to avoid progression to invasive disease. A preemptive approach is sometimes used for antifungal therapy. (See "Treatment and prevention of invasive aspergillosis", section on 'Preemptive therapy' and "Treatment of neutropenic fever syndromes in adults with hematologic malignancies and hematopoietic cell transplant recipients (high-risk patients)", section on 'Pre-emptive antifungal therapy'.)

TEMPERATURE MEASUREMENT

An elevated body temperature is the trigger for initiating an aggressive protocol of neutropenic fever management. (See "Treatment of neutropenic fever syndromes in adults with hematologic malignancies and hematopoietic cell transplant recipients (high-risk patients)" and "Treatment and prevention of neutropenic fever syndromes in adult cancer patients at low risk for complications".)

Since the decision of whether to initiate the neutropenic fever management pathway may be based upon the difference of half a degree Celsius [24], the reliability of the procedure used to measure body temperature is extremely important. On the one hand, the risk of serious complications in high-risk patients who are not treated promptly is substantial. On the other hand, the potential toxicity of antimicrobial agents, the potential impact of antimicrobial use on resistance, and the costs of hospitalization and antimicrobial therapy are significant factors. It is therefore critical to accurately assess body temperature in order to aggressively treat patients with neutropenic fever and to avoid the overtreatment of stable neutropenic patients who do not have a fever.

There is no universally preferred method for measuring body temperature [25], and the method used varies by institution. Most medical facilities use oral, infrared tympanic membrane, axillary, or rectal thermometry as a surrogate of core body temperature.

We favor oral thermometry in patients without oral mucositis, and tympanic membrane thermometry or axillary thermometry in patients with oral mucositis. Each of these methods has shortcomings, and the use of each method requires that proper technique be used to obtain accurate results [7]. Peripheral methods of monitoring temperature (tympanic membrane, temporal artery, axillary, and oral thermometry) do not accurately reflect core body temperature as measured by central methods (pulmonary artery catheter, urinary bladder, esophageal, and rectal thermometry) and are less sensitive [26]; however, central methods are not practical or safe in neutropenic patients.

The following issues apply to the use of the various thermometry techniques in neutropenic patients:

- Oral thermometry is the most common method for measuring temperature. However, in neutropenic patients with oral mucositis, oral thermometry may be painful and may overestimate body temperature compared with tympanic membrane thermometry [25].
- Infrared tympanic membrane thermometry is noninvasive and convenient. However, falsely high readings may be obtained from the dependent ear [27,28] and falsely low readings may occur if cerumen is present in the external auditory canal [7,29]. Compared with direct measurement of core body temperature by pulmonary artery catheter readings, falsely low tympanic thermometry that might delay medical interventions have been observed in up to 21 percent of cases [27]. Conversely, falsely high readings that might compel unnecessary interventions have been observed in up to 38 percent of patients whose temperatures were taken with a tympanic thermometer [27]. Inconsistencies in operator technique and equipment maintenance also contribute to inaccuracies [30-32].
- Like tympanic membrane thermometry, axillary thermometry may also result in falsely low or falsely high measurements [27,33].
- Rectal thermometry is **not** recommended in neutropenic or thrombocytopenic patients because it may increase the risk for local mucosal trauma-induced bacteremia and bleeding.

The pathogenesis and treatment of fever are discussed separately. (See "Pathophysiology and treatment of fever in adults".)

PATHOGENESIS

Contributory factors to the pathogenesis of neutropenic fever include [2]:

- The direct effects of chemotherapy on mucosal barriers and the immune system
- Breeches in host defenses related to the underlying malignancy

Chemotherapy-induced mucositis occurs throughout the alimentary system, and seeding of the bloodstream from endogenous flora in the gastrointestinal tract is believed to cause the majority of episodes of neutropenic fever (see "Oral toxicity associated with chemotherapy" and "Enterotoxicity of chemotherapeutic agents"). Obstruction of lymphatic channels, the biliary tract, and/or bronchial, gastrointestinal, or urinary systems by tumor(s) or as a result of surgical procedures are also common causes of infection.

Immune defects related to underlying hematologic disorders, in addition to the immunosuppressive effects of chemotherapy, also place patients at higher risk for infection [34]. In one study, patients who developed severe infection or died had a significant decrease in phagocytic activity of neutrophils compared with those with only a mild infection, suggesting that neutrophils might be preactivated and have reduced function prior to the initiation of chemotherapy [35]. In addition, the administration of chemotherapy not only decreases the number of neutrophils but also results in chemotactic and phagocytic defects.

Risk of infection based on type of malignancy — 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, and splenectomized (including functional asplenia) patients results in an increased risk of sepsis from encapsulated organisms, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*, as well as from *Capnocytophaga canimorsus* and *Babesia* spp. (See "Clinical features, evaluation, and management of fever in patients with impaired splenic function", section on 'Important pathogens'.)

- The T cell defects associated with lymphoma result in an increased risk of infection with intracellular pathogens, such as *Listeria monocytogenes*, *Salmonella* spp, *Cryptococcus neoformans*, and *Mycobacterium tuberculosis*. Patients with acute lymphocytic leukemia, central nervous system tumors, and other cancer patients receiving high-dose glucocorticoids are at increased risk for *Pneumocystis jirovecii* (formerly *P. carinii*) pneumonia. (See "Epidemiology and pathogenesis of Listeria monocytogenes infection" and "Nontyphoidal Salmonella: Microbiology and epidemiology" and "Microbiology and epidemiology of Cryptococcus neoformans infection" and "Epidemiology of tuberculosis" and "Epidemiology, clinical manifestations, and diagnosis of Pneumocystis pneumonia in HIV-uninfected patients".)

- The risk of bacterial infection varies by the underlying malignant disease diagnosis and by the associated treatments for those malignancies [23].

EPIDEMIOLOGY

An infectious source is identified in approximately 20 to 30 percent of febrile neutropenic episodes [2,36]. Often the only evidence of infection is bacteremia, which is documented in 10 to 25 percent of patients [2]. Approximately 80 percent of identified infections are believed to arise from the patient's endogenous flora [37]. The following table lists the range of pathogens found in patients with chemotherapy-induced neutropenia (table 3).

Bacterial pathogens — Gram-negative bacilli, particularly *Pseudomonas aeruginosa*, were the most commonly identified pathogens in neutropenic patients until the 1980s [38]. Subsequently, gram-positive bacteria have become the most common pathogens [39,40]. Common gram-positive cocci include *Staphylococcus epidermidis* (by far the most common), *Staphylococcus aureus*, and streptococci; less common gram-positive organisms include *Corynebacterium jeikeium*, *Bacillus* spp, *Leuconostoc* spp, *Lactobacillus* spp, *Cutibacterium* (formerly *Propionibacterium*) *acnes*, and *Rhodococcus* spp [41].

A number of changes in practice likely accounted for the trend toward gram-positive infections, including the introduction of long-term indwelling central venous catheters [42], the use of empiric antibiotic regimens for neutropenic fever designed to cover *P. aeruginosa*, the use of prophylactic antimicrobials that are primarily active against gram-negative pathogens (eg, ciprofloxacin), and newer chemotherapeutic regimens.

However, more recently, the shift from gram-negative bacteria to gram-positive bacteria in documented infections observed during the pre-2000 period has been replaced by a trend back toward gram-negative bacteria, with the emergence of antibiotic-resistant gram-negative strains from bloodstream isolates from neutropenic cancer patients [43-46]. However, the ratio of gram-positive to gram-negative bacteria as the cause of bacteremia in cancer patients remains at approximately 60:40 [43,47].

In a study from the Multinational Association for the Supportive Care in Cancer (MASCC) of 2142 high- and low-risk patients with chemotherapy-related neutropenic fever, there were 499 bacteremias (23 percent) [48]. Gram-positive organisms accounted for 57 percent of cases, gram-negative organisms for 34 percent, and polymicrobial bacteremia for 10 percent.

The following observations have been made about bacterial infections in neutropenic patients:

- Bacteria are the most frequent infectious causes of neutropenic fever [49].

- Gram-negative bacteria (eg, *P. aeruginosa*) are generally associated with the most serious infections.

- *S. epidermidis* is the most common gram-positive pathogen, accounting for approximately one-half of all infections due to gram-positive infections. It is much less virulent than other bacterial pathogens [47].

- Among gram-positive bacteria, *S. aureus* (particularly methicillin-resistant strains), some viridans streptococci, and enterococci (particularly vancomycin-resistant strains) can cause serious infections [40]. In some European cancer centers, methicillin resistance has dominated among *S. aureus* bloodstream isolates [50].

- Although anaerobic bacteria are abundant in the alimentary tract, they are infrequent pathogens isolated from patients with neutropenic fever. However, they can contribute to the pathogenesis of necrotizing mucositis, sinusitis, periodontal cellulitis, perirectal cellulitis, intra-abdominal or pelvic infection, and neutropenic enterocolitis (typhlitis) and can cause anaerobic bacteremia.

- Polymicrobial infections are infrequent, but their frequency appears to be rising [49].

Fungal pathogens — Fungal pathogens are common in high-risk patients with neutropenic fever (table 1) but are uncommon in low-risk patients. The risk for invasive fungal infections increases with the duration and severity of neutropenia, prolonged antibiotic use, and number of chemotherapy cycles. Fungi are rarely the cause of the first febrile episode in neutropenic patients [51]. More commonly, invasive fungal infections occur later as a cause of persistent or recurrent neutropenic fever. However, fungal infections can occasionally present early or even prior to initial chemotherapy.

In an autopsy study of patients who died after prolonged febrile neutropenia between 1966 and 1975, 69 percent of patients had evidence of invasive fungal infections [52]. It is important to note that this study was done before either antifungal prophylaxis or early diagnosis and treatment of invasive fungal infections was routine. Also, diagnostic methods have improved over time.

The following observations have been made about fungal infections in general and about specific fungal pathogens:

- Fungi are rarely identified as the cause of initial fever during neutropenia. More commonly, they are identified as causes of persistent or recurrent fever beyond the first week of neutropenia.

- *Candida* spp and *Aspergillus* spp account for most invasive fungal infections during neutropenia. The former are acquired through gastrointestinal tract colonization and translocation across damaged intestinal epithelial surface. The latter are acquired by inhalation of airborne spores (conidia) into the upper and lower respiratory tract followed by germination and invasive hyphal growth.

- Fever is often the sole manifestation of candidemia. Erythematous macronodular skin nodules may occur in some patients with candidemia. The reported median time of candidemia following standard remission-induction therapy for acute myelogenous leukemia (AML) has been 16 days (range 13 to 25 days) from the first day of the cytotoxic regimen, coincident with the time of maximum cytotoxic therapy-induced intestinal epithelial damage [53]. Among patients who develop disseminated candidiasis following chemotherapy, hepatosplenic involvement is common; signs and symptoms are often

not present until the neutropenia resolves. The reported median time to a diagnosis of hepatosplenic involvement after AML induction therapy has been 26 days (range 19 to 31 days) from the first day of the cytotoxic regimen [53]. (See "Epidemiology and pathogenesis of candidemia in adults" and "Chronic disseminated candidiasis (hepatosplenic candidiasis)".)

- *Candida albicans* accounts for the majority of candidemias; *C. glabrata*, *C. tropicalis*, and other *Candida* spp account for the remainder. A higher proportion of candidemias are due to non-albicans *Candida* species when fluconazole prophylaxis has been administered. (See "Epidemiology and pathogenesis of candidemia in adults", section on 'Prevalence of Candida species'.)
- *Candida* spp are common fungal causes of central venous catheter-associated infections and can cause disseminated candidiasis. (See "Clinical manifestations and diagnosis of candidemia and invasive candidiasis in adults", section on 'Clinical manifestations' and "Management of candidemia and invasive candidiasis in adults", section on 'Central venous catheter removal'.)
- *Aspergillus* spp is a common fungal pathogen in immunocompromised hosts, and infection follows the inhalation of conidia (spores); manifestations primarily affect the lower respiratory tract (pneumonia) and upper respiratory tract (sinusitis) but may also involve the central nervous system, bones, and skin. (See "Epidemiology and clinical manifestations of invasive aspergillosis".)
- The agents of mucormycosis can cause life-threatening rhino-orbital-cerebral, pulmonary, and disseminated infections in immunocompromised hosts, particularly those with uncontrolled hyperglycemia due to pre-existing diabetes mellitus or administration of glucocorticoids. (See "Mucormycosis (zygomycosis)".)
- *Fusarium* spp have been increasingly reported to cause invasive fungal infections in patients with hematologic malignancies with prolonged severe neutropenia or significant glucocorticoid exposure. (See "Mycology, pathogenesis, and epidemiology of Fusarium infection", section on 'Immunocompromised patients'.)
- New infection or reactivation infection with endemic fungi (*Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides* spp) should also be considered in patients who have lived in or traveled to endemic areas, particularly in the setting of prolonged glucocorticoid use or other immunosuppression. (See "Pathogenesis and clinical features of pulmonary histoplasmosis", section on 'Epidemiology' and "Pathogenesis and clinical manifestations of disseminated histoplasmosis", section on 'Risk factors' and "Primary pulmonary coccidioidal infection", section on 'Epidemiology' and "Mycology, pathogenesis, and epidemiology of blastomycosis", section on 'Epidemiology'.)

Prophylaxis and empiric therapy of invasive fungal infections in high-risk patients (table 1) are discussed in detail separately. (See "Prophylaxis of invasive fungal infections in adults with hematologic malignancies" and "Treatment of neutropenic fever syndromes in adults with hematologic malignancies and hematopoietic cell transplant recipients (high-risk patients)", section on 'Addition of an antifungal agent'.)

Viral pathogens — Viral infections, especially human herpesviruses, are common in high-risk patients with chemotherapy-induced neutropenia (table 1) and are effectively prevented with antiviral prophylaxis. (See "Prophylaxis of infection during chemotherapy-induced neutropenia in high-risk adults".)

Most herpes simplex virus (HSV)-1 and -2 infections in adults are due to reactivation of latent infections in seropositive patients. The likelihood of reactivation is influenced by the intensity of the chemotherapy regimen and by the relative impact upon virus-specific cytotoxic T-lymphocyte-mediated host defenses. Reactivation occurs in two-thirds of seropositive patients undergoing induction chemotherapy for AML and those undergoing hematopoietic cell transplantation (HCT) in the absence of antiviral prophylaxis [54,55]. Ulcerations of the oral or esophageal mucosa and ulcers or vesicles of lips, genitalia, skin, or perianal areas are the most common manifestations. HSV can cause a wide variety of syndromes, including encephalitis, meningitis, myelitis, esophagitis, pneumonia, hepatitis, erythema multiforme, and ocular disease.

Herpes zoster, which is caused by varicella-zoster virus, often presents in an atypical disseminated pattern involving multiple dermatomes or widespread skin dissemination in immunocompromised hosts. The reported median time to reactivation of herpes zoster in lymphoma patients has been approximately five months following initiation of chemotherapy (range 0.4 to 51.3 months) [56]. Immunocompromised patients with disseminated varicella-zoster virus infection can have pulmonary involvement and should be placed on respiratory precautions to prevent aerosolized transmission to susceptible individuals.

Reactivation or, less commonly, primary acquisition of other human herpesviruses (Epstein-Barr virus, cytomegalovirus, or human herpesvirus 6 A or B) can also occur in this patient population as a result of immunosuppression or receipt of blood products or stem cells, respectively. Allogeneic HCT recipients are at particularly high risk for these infections. (See "Overview of infections following hematopoietic cell transplantation".)

Infections caused by community-acquired respiratory viruses (CARVs) are a significant threat to patients with hematologic malignancies and stem cell transplantation [57-59]. CARVs have been documented with increasing frequency and occur commonly in neutropenic patients; these include influenza virus, respiratory syncytial virus, parainfluenza viruses types I to IV, human adenovirus, human rhinoviruses, human coronaviruses, and human metapneumovirus. The risk for infection by these organisms tends to coincide with respiratory virus outbreaks in the general population. Although information on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), in cancer patients and organ transplant recipients is limited, reports suggest that the severity of the infection may be greater, particularly among those with active comorbidities [60,61]. The severity of CARV infections in general, and, specifically, the rate of progression from upper respiratory tract disease to lower respiratory tract disease are dependent on degree, duration, and type of immunosuppression. SARS-CoV-2 is also potential cause of neutropenic fever. (See "Epidemiology of influenza" and "Respiratory syncytial virus infection: Clinical features and diagnosis" and "Parainfluenza viruses in adults" and "Pathogenesis, epidemiology, and clinical manifestations of adenovirus infection" and "Human metapneumovirus infections".)

Other — Reactivation of tuberculosis should be considered in patients with epidemiologic risk factors, especially in those with prolonged glucocorticoid use or other forms of immunosuppression that increase the risk (eg, a tumor necrosis factor-alpha inhibitor). *Babesia microti* or *B. divergens* infection can cause overwhelming sepsis in patients with compromised splenic function. (See "Epidemiology of tuberculosis" and "Tumor necrosis factor-alpha inhibitors and mycobacterial infections" and "Babesiosis: Microbiology, epidemiology, and pathogenesis".)

MANAGEMENT

It is critical to recognize neutropenic fever early and to initiate empiric systemic antibacterial therapy promptly in order to avoid progression to a sepsis syndrome and possibly death. In all cancer patients presenting with neutropenic fever, empiric antibacterial therapy should be initiated immediately after blood cultures have been obtained and before any other investigations have been completed. (See "Treatment of neutropenic fever syndromes in adults with hematologic malignancies and hematopoietic cell transplant recipients (high-risk patients)" and "Treatment and prevention of neutropenic fever syndromes in adult cancer patients at low risk for complications".)

Initial assessment — A reliable method for obtaining body temperature must be used and a mechanism for estimating the absolute neutrophil count (ANC) is mandatory (see 'Temperature measurement' above and 'Neutropenia' above). The risk of neutropenia, the risk of complications from neutropenic fever, and the risk of sepsis must be assessed quickly. These issues are discussed in greater detail separately. (See "Risk assessment of adults with chemotherapy-induced neutropenia" and "Treatment of neutropenic fever syndromes in adults with hematologic malignancies and hematopoietic cell transplant recipients (high-risk patients)", section on 'Initial assessment' and "Treatment and prevention of neutropenic fever syndromes in adult cancer patients at low risk for complications", section on 'Initial assessment'.)

Patients and their families should be instructed by their oncologist to inform health care providers in the triage setting about recent chemotherapy, and providers in the triage setting should ask cancer patients who do not offer this information about recent chemotherapy. Receipt of systemic antineoplastic therapy within the preceding six weeks has been advocated for use in emergency triage departments to identify patients who are likely to be neutropenic.

Timing of antibiotics — Antibiotics should be given as early as possible. The guidelines of the Infectious Diseases Working Party of the German Society of Hematology and Oncology and the Northern Ireland Cancer Network recommend that empiric broad-spectrum antibacterial therapy be initiated immediately after blood cultures have been obtained and before any other investigations have been completed in all patients with neutropenic fever [11,62]. International guidelines advocate the administration of empiric antibacterial therapy within **60 minutes** of presentation in all patients presenting with a neutropenic fever (algorithm 1) [23,62-64]. We agree with both of these recommendations. Some investigators have argued that initial empiric antimicrobial therapy should be administered within 30 minutes [65].

The optimal timing for the administration of the first dose of empiric antibacterial therapy in patients with neutropenic fever in order to prevent harm is not known. Early studies of patients with neutropenic fever documented mortality rates of up to 70 percent if initiation of antibiotics was delayed [66]. In a retrospective cohort study of 2731 patients with septic shock (only 7 percent of whom were neutropenic), each hour delay in initiating effective antimicrobials decreased survival by approximately 8 percent [67]. The in-hospital mortality among adult patients with severe sepsis or septic shock decreased from 33 to 20 percent (odds ratio 0.30, 95% CI 0.11-0.83) when the time from triage to appropriate antimicrobial therapy was one hour or less compared with more than one hour [68]. One cohort study observed that each hour delay in the time to empiric antibacterial administration in febrile neutropenic patients increased the 28-day mortality by 18 percent [65].

Although some investigators have reported the importance of protocol compliance, including timely administration of empiric antibiotics, for lowering complication rates and mortality [69-71], a large cohort study of low-risk febrile neutropenic cancer patients failed to demonstrate a survival benefit of early initiation of empiric antibacterial therapy [72]. However, this population was at low risk for mortality (2.8 percent) with low incidences of microbiologically documented infection (12 percent) and resistant pathogens (6 percent). The ability to detect a protocol-driven impact on outcomes such as mortality may have been obscured in this study. Moreover, it was not possible to control for the duration of clinical illness before the patients presented for triage [73]. The weight of evidence continues to support early and appropriate initial empiric antibiotic therapy to enhance the chances of therapeutic success.

The successful management of neutropenic fever and sepsis syndromes is a time-dependent process analogous to acute stroke or ST-segment elevation myocardial infarction syndromes [62]. There is a spectrum of the severity of the illness. In one multicenter observational French study using standard definitions, 55 percent of febrile neutropenic cancer patients presenting to emergency departments had a defined sepsis syndrome and almost one-half (45 percent) had evidence of a severe sepsis syndrome or septic shock [74]. Approximately 2 to 5 percent of febrile neutropenic patients seeking medical care from the emergency department require critical care services [75-77]. In another European longitudinal observational study of patients requiring critical care services, severe sepsis or septic shock was more commonly observed among patients with hematologic malignancies (59 percent) than among those with solid tumors (24 percent) or those without an underlying cancer (25 percent) [78].

The reported median times from assessment of febrile neutropenic cancer patients in an emergency department setting to the initiation of empiric antibacterial therapy have ranged widely from 15 minutes to over 9 hours [9,72,75,79-83]. Audits from the United Kingdom reported that only 18 to 26 percent of patients received initial empiric antibacterial therapy within the one-hour "door-to-needle" target timeframe [9,82]. The most common reasons for failure to comply with this timeframe have included failure to administer the initial dose of the empiric antibacterial regimen until the patient has been transferred from the emergency department to the inpatient ward, prolonged time between arrival and clinical assessment, lack of awareness of the natural history of neutropenic fever syndromes and their evolution to severe sepsis or shock, failure of the emergency department to stock the appropriate antibacterial therapy, and neutropenic fever protocols not being readily available in the emergency department for quick reference [9]. A systematic algorithm-driven approach to the febrile neutropenic patient who presents to an emergency department that includes the use of standardized order sets reduces the time from triage to antibiotic administration by up to two-thirds [83,84].

Nonspecific presentation — The febrile neutropenic patient who is developing neutropenic fever or sepsis syndrome may seek medical attention with nonspecific symptoms [85] and may manifest muted signs of an inflammatory process [1]. Laboratory confirmation of neutropenia may not return within the recommended timeframe of one hour. Accordingly, the index of suspicion for infection must often be based upon limited patient history, the likelihood that the patient is neutropenic relative to the history of administration of antineoplastic therapy or of the underlying malignancy, and vital signs. (See "Treatment of neutropenic fever syndromes in adults with hematologic malignancies and hematopoietic cell transplant recipients (high-risk patients)", section on 'Risk of neutropenia'.)

Diagnostic evaluation — Once empiric antibacterial therapy has been started, all patients should have a thorough history and detailed physical examination as well as laboratory, microbiology, and imaging studies (table 4). This is discussed in detail separately. (See "Diagnostic approach to the adult cancer patient with neutropenic fever".)

Treatment regimens — The aim of empiric therapy is to cover the most likely and most virulent pathogens that may rapidly cause serious or life-threatening infection in neutropenic patients (table 3) [2]. Although antimicrobial agents are usually administered empirically, they should always include appropriate coverage for suspected or known infections. Even when the pathogen is known, the regimen should provide broad-spectrum empiric coverage

for the possibility of other pathogens, unlike the treatment strategy adopted in many immunocompetent hosts. Initial regimen selection should be guided by the patient's history, allergies, symptoms, signs, recent antimicrobial agent use and culture data, and awareness of the susceptibility patterns of institutional nosocomial pathogens [86]. Consideration of the risk of resistant organisms has emerged as a factor that impacts the choice of empiric therapy and targeted therapy once a pathogen has been identified, as well as outcomes.

Specific treatment regimens for patients presenting with neutropenic fever who are high risk or low risk for serious complications are discussed separately. (See "Treatment of neutropenic fever syndromes in adults with hematologic malignancies and hematopoietic cell transplant recipients (high-risk patients)" and "Treatment and prevention of neutropenic fever syndromes in adult cancer patients at low risk for complications".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Neutropenic fever in adults with cancer".)

INFORMATION FOR PATIENTS

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

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

- Basics topics (see "Patient education: When to worry about a fever in adults (The Basics)" and "Patient education: Neutropenia and fever in people being treated for cancer (The Basics)")

SUMMARY

- Cancer patients receiving cytotoxic antineoplastic therapy sufficient to adversely affect myelopoiesis and the integrity of the gastrointestinal mucosa are at risk for invasive infection due to colonizing bacteria and/or fungi that translocate across intestinal mucosal surfaces. Since the magnitude of the neutrophil-mediated component of the inflammatory response may be muted in neutropenic patients, a fever may be the earliest and only sign of infection. It is critical to recognize neutropenic fever early and to initiate empiric systemic antibacterial therapy promptly in order to avoid progression to a sepsis syndrome and possibly death. (See 'Introduction' above.)
- Fever in neutropenic patients is defined as a single oral temperature of >38.3°C (101°F) or a temperature of >38.0°C (100.4°F) sustained for >1 hour. (See 'Fever' above.)
- Severe neutropenia is usually defined as an absolute neutrophil count (ANC) <500 cells/microL or an ANC that is expected to decrease to <500 cells/microL over the next 48 hours (calculator 1). The risk of clinically important infection rises as the neutrophil count falls below 500 cells/microL. (See 'Neutropenia' above.)
- It is crucial to assess the risk for serious complications in patients with neutropenic fever, since this assessment will dictate the approach to therapy, including the need for inpatient admission, intravenous antibiotics, and prolonged hospitalization. (See 'Risk of serious complications' above.)
- Low-risk patients with neutropenic fever are those in whom the duration of neutropenia (ANC <500 cells/microL) is expected to be ≤7 days and those with no comorbidities or evidence of significant hepatic or renal dysfunction. Most patients receiving chemotherapy for solid tumors or lymphoma are considered to be low risk. (See 'Risk of serious complications' above.)
- We define high-risk patients with neutropenic fever as those who are expected to be neutropenic (ANC <500 cells/microL) for >7 days. Patients with neutropenic fever who have ongoing comorbidities or evidence of significant hepatic or renal dysfunction are also considered to be high risk, regardless of the duration of neutropenia. Other criteria that confer a high-risk status can be found in the table (table 1). Profound prolonged neutropenia (ie, ANC ≤100 cells/microL expected to last >7 days) is most likely to occur in the pre-engraftment phase of hematopoietic cell transplantation (particularly allogeneic) and in patients undergoing induction chemotherapy for acute leukemia (table 2). (See 'Risk of serious complications' above.)
- An infectious source is identified in approximately 20 to 30 percent of febrile neutropenic episodes. Often the only evidence of infection is bacteremia, which is documented in 10 to 25 percent of patients. Approximately 80 percent of identified infections are believed to arise from the patient's endogenous flora. Gram-positive bacteria are the most common causes of infection in neutropenic patients, but gram-negative bacteria (eg, *Pseudomonas aeruginosa*) are generally associated with the most serious infections. The following table lists the range of pathogens found in patients with chemotherapy-induced neutropenia (table 3). (See 'Epidemiology' above.)
- Fungal pathogens are more common in high-risk patients with prolonged persistent or recrudescent neutropenic fever syndromes but are uncommon in low-risk patients. *Candida* and *Aspergillus* spp account for most invasive fungal infections during neutropenia. (See 'Fungal pathogens' above.)
- A reliable method for obtaining body temperature must be used, and a mechanism for estimating the ANC is mandatory (see 'Temperature measurement' above and 'Neutropenia' above). The risk of neutropenia, the risk of complications from neutropenic fever, and the risk of sepsis must be assessed quickly. (See "Treatment of neutropenic fever syndromes in adults with hematologic malignancies and hematopoietic cell transplant recipients (high-risk patients)", section on 'Initial assessment'.)

- Patients and their families should be instructed by their oncologist to inform health care providers in the triage setting about recent chemotherapy, and providers in the triage setting should ask cancer patients who do not offer this information about recent chemotherapy. Receipt of systemic antineoplastic therapy within the preceding six weeks has been advocated for use in emergency triage departments to identify patients who are likely to be neutropenic. (See 'Initial assessment' above.)

- In all patients presenting with neutropenic fever, empiric initial broad-spectrum antibacterial therapy should be initiated immediately after blood cultures have been obtained and before any other investigations have been completed. Empiric antibacterial therapy should be started within 60 minutes of presentation in all patients presenting with neutropenic fever (algorithm 1). Some investigators have argued that initial empiric antimicrobial therapy should be administered within 30 minutes; we agree that antibiotics should be given as early as possible. (See 'Timing of antibiotics' above.)

- Once empiric antibacterial therapy has been started, all patients should have a careful history and detailed physical examination as well as laboratory, microbiology, and imaging studies (table 4). (See "Diagnostic approach to the adult cancer patient with neutropenic fever".)

- Specific treatment regimens for high-risk and low-risk patients presenting with neutropenic fever are discussed separately. (See "Treatment of neutropenic fever syndromes in adults with hematologic malignancies and hematopoietic cell transplant recipients (high-risk patients)" and "Treatment and prevention of neutropenic fever syndromes in adult cancer patients at low risk for complications".)

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Topic 16708 Version 34.0

GRAPHICS

Patients with chemotherapy-induced neutropenic fever who are at high risk for serious complications

Patients with **any** of the following characteristics are considered to be at high risk for serious complications during episodes of neutropenic fever:
Receipt of cytotoxic therapy sufficiently myelosuppressive to result in anticipated severe neutropenia (ANC <500 cells/mcL) for >7 days*
MASCC risk index score <21 Δ
CISNE score of ≥3 Δ (in patients with solid tumors)
Presence of any active uncontrolled comorbid medical problems, including, but not limited to: ▪ Signs of severe sepsis or septic shock (eg, hemodynamic instability, mental status changes of new onset, respiratory dysfunction, oliguria) ▪ Oral or gastrointestinal mucositis that interferes with swallowing or causes severe diarrhea ▪ Gastrointestinal symptoms, including abdominal pain, nausea and vomiting, or diarrhea ▪ Intravascular catheter infection, especially catheter tunnel infection ▪ New pulmonary infiltrate or hypoxemia ▪ Underlying chronic lung disease ▪ Complex infection at the time of presentation
Alemtuzumab or CAR-T cell use within the past two months
Uncontrolled or progressive cancer ¶
Evidence of hepatic insufficiency (defined as aminotransferase levels >5 times normal values) or renal insufficiency (defined as a creatinine clearance of <30 mL/minute)

ANC: absolute neutrophil count; MASCC: Multinational Association for Supportive Care in Cancer; CISNE: Clinical Index of Stable Febrile Neutropenia; CAR: chimeric antigen receptor.
* The authors use an anticipated ANC threshold of <500 cells/microL for >7 days to consider a patient at high risk for serious complications. It should be noted that the Infectious Diseases Society of America and the National Comprehensive Cancer Network guidelines use an ANC threshold of ≤100 cells/microL for >7 days[1,2]. At the time that the patient presents with neutropenic fever, it is not always possible to anticipate whether the patient will have severe neutropenia (<500 cells/microL) for >7 days. Clinical circumstances that are likely to result in severe neutropenia for >7 days put patients at high risk for serious complications; these criteria are most likely to be met following induction chemotherapy for acute leukemia and during the pre-engraftment phase of myeloablative hematopoietic cell transplantation (particularly allogeneic).
¶ Defined as any leukemic patient not in complete remission or a nonleukemic patient with evidence of disease progression after more than two courses of chemotherapy.
Δ Refer to the associated UpToDate topic review for details about the MASCC risk index and the CISNE score.

Data adapted from:

1. *Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2011; 52:e56.*
2. *National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Prevention and treatment of cancer-related infections. Version 1.2018. Available at: http://www.nccn.org (Accessed on August 01, 2018).*
3. *Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America clinical practice guideline update. J Clin Oncol 2018; 36:1443.*

Graphic 67027 Version 14.0

Factors to consider in assessing risk of an episode of neutropenic fever in patients undergoing cytotoxic chemotherapy for malignancy

Factors related to	Factor	Effect on risk	
Patient characteristics	▪ Advanced age	▪ Risk increases if age ≥65 years[1]	
	▪ Performance status	▪ Risk increases if ECOG performance score ≥2[1]	
	▪ Nutritional status	▪ Risk increases if albumin <35 g/L[2,3]	
	▪ Prior neutropenic fever episode	▪ Risk in cycles 2 to 6 is fourfold greater if neutropenic fever episode occurs in cycle 1[4]	
	▪ Comorbidities	▪ Neutropenic fever odds increase by 27, 67, and 125% for one, two, or three or more comorbidities, respectively[1,5]	
Underlying malignancy	▪ Cancer diagnosis	**Diagnosis**	**Reported neutropenic fever rates (%)**
		▪ Acute leukemia/MDS	85.0 to 95.0[6-9]
		▪ High-grade lymphoma	35.0 to 71.0*[10]
		▪ Soft tissue sarcoma	27.0 (95% CI 19.0-34.5)[4,5,11,12]
		▪ NHL/myeloma	26.0 (95% CI 22.0-29.0)[4,5,11,12]
		▪ Germ cell carcinoma	23.0 (95% CI 16.6-29.0)[4,5,11,12]
		▪ Hodgkin lymphoma	15.0 (95% CI 6.6-24.0)[4,5,11,12]
		▪ Ovarian carcinoma	12.0 (95% CI 6.6-17.7)[4,5,11,12]
		▪ Lung cancers	10.0 (95% CI 9.8-10.7)[4,5,11,12]
		▪ Colorectal cancers	5.5 (95% CI 5.1-5.8)[4,5,11,12]
		▪ Head and neck carcinoma	4.6 (95% CI 1.0-8.2)[4,5,11,12]
		▪ Breast cancer	4.4 (95% CI 4.1-4.7)[4,5,11,12]
		▪ Prostate cancer	1.0 (95% CI 0.9-1.1)[4,5,11,12]
	▪ Cancer stage	▪ Risk increases for advanced stage (≥2)[4]	
	▪ Remission status	▪ Risk increases if not in remission[8,13]	
	▪ Cancer treatment response	▪ Risk is lowest if patient has a CR ▪ If patient has a PR, neutropenic fever risk is greater for acute leukemia than for solid tissue malignancies[8] ▪ Neutropenic fever risk is higher in patients with persistent, refractory, or progressive disease despite treatment[14,15]	
Treatment of malignancy	▪ Cytotoxic regimen	Risk is higher with regimens that include: ▪ Anthracyclines at doses ≥90 mg/m^2 ▪ Cisplatin at doses ≥100 mg/m^2 ▪ Ifosfamide at doses ≥9 g/m^2 ▪ Cyclophosphamide at doses ≥1 g/m^2 ▪ Etoposide at doses ≥500 mg/m^2 ▪ Cytarabine at doses ≥1 g/m^2 ▪ High dose density ▪ Anthracycline + taxane, and cyclophosphamide or gemcitabine, for breast cancer	
	▪ Dose intensity	▪ Increased risk if >85% of scheduled doses are administered[12,16]	
	▪ Degree and duration of GI and/or oral mucositis	▪ Risk is greatest if NCI mucositis grade is ≥3 (GI) or if peak score on OMAS is ≥2[9,17,18]	
	▪ Degree and duration of cytopenia	▪ Profound, protracted neutropenia	ANC <100/mcL for ≥7 days[19-21]
		▪ Lymphopenia	ALC <700/mcL (ANC surrogate)[11,22]
		▪ Monocytopenia	AMC <150/mcL (ANC surrogate)[23]

ECOG: Eastern Cooperative Oncology Group; MDS: myelodysplastic syndrome; NHL: non-Hodgkin lymphoma; CR: complete response; PR: partial response; GI: gastrointestinal; NCI: National Cancer Institute; OMAS: oral mucositis assessment scale; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; AMC: absolute monocyte count.
* Grade 3 and 4 neutropenia. Treatment included colony-stimulating factors and antimicrobial prophylaxis. Rate of neutropenia varied by chemotherapy regimen.

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From: Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. J Clin Oncol 2018; 36:3043. Reprinted with permission.

Graphic 119454 Version 2.0

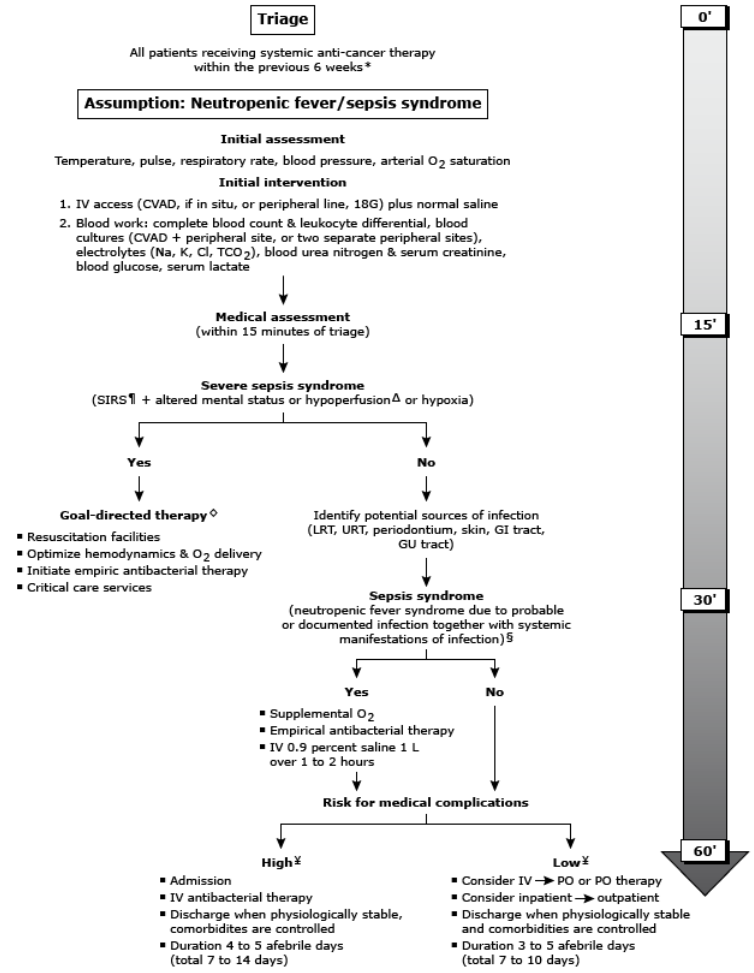
Range of pathogens encountered in febrile neutropenic patients

Commonly cultured organisms	Less commonly cultured organisms	Additional organisms
Gram-negative bacteria	**Gram-negative bacteria**	**Fungi**
Escherichia coli	*Proteus* spp	*Cryptococcus* spp
Klebsiella spp	*Haemophilus* spp	*Histoplasma capsulatum*
Enterobacter spp	*Serratia* spp	*Coccidioides* spp
Pseudomonas aeruginosa	*Neisseria meningitidis*	Mucorales
Citrobacter spp	*Capnocytophaga canimorsus*	*Pneumocystis jirovecii* (formerly *P. carinii*)
Acinetobacter spp	*Legionella* spp	**Viruses**
Stenotrophomonas maltophila	*Moraxella* spp	Herpes simplex virus 1,2
Gram-positive bacteria	**Gram-positive bacteria**	Varicella-zoster virus
Coagulase-negative staphylococci	*Bacillus* spp	Cytomegalovirus
Staphylococcus aureus	*Listeria monocytogenes*	Epstein-Barr virus
Enterococcus spp	*Stomatococcus* spp	Human herpesvirus 6
Viridans group streptococci	*Corynebacterium jeikeium*	Enteroviruses
Streptococcus pneumoniae		Respiratory syncytial virus
Streptococcus pyogenes		Influenza virus
Other bacteria		Parainfluenza virus
Clostridioides (formerly *Clostridium*) *difficile*		**Other**
Anaerobes		*Babesia* spp
Mycobacteria		*Plasmodium* spp (the cause of malaria)
Fungi		*Toxoplasma* spp
Aspergillus spp		*Strongyloides stercoralis*
Candida spp		*Nocardia* spp

Adapted from: Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guidelines for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2011; 52:e56.

Graphic 63465 Version 21.0

Time-dependent algorithm for the initial assessment and management of cancer patients with neutropenic fever and suspected sepsis syndrome



CVAD: central venous access device; Na: sodium; K: potassium; Cl: chloride; TCO_2: total carbon dioxide; SIRS: systemic inflammatory response syndrome; LRT: lower respiratory tract; URT: upper respiratory tract; GI: gastrointestinal tract; GU: genitourinary tract; O_2: oxygen; IV: intravenous; MASCC: Multinational Association for Supportive Care in Cancer; PO: per os (by mouth).

* The Northern Ireland Cancer Network states that neutropenic sepsis is a "time-dependent" condition, the successful management of which is dependent upon the early recognition of the likelihood that the cancer patient's problem represents a neutropenic fever/sepsis syndrome[1]. Since more than 70 percent of cancer treatment-related syndromes, including neutropenic fever, manifest within four to six weeks of systemic treatment[2], the Northern Ireland Cancer Network has recommended a history of chemotherapy within the past six weeks as a sensitive discriminator to detect patients with neutropenic fever/sepsis syndromes by triage services in health care facilities[1].

¶ SIRS is a clinical syndrome that is a form of dysregulated inflammation. The term SIRS has routinely been associated with both infectious processes (sepsis) and noninfectious insults, such as an autoimmune disorder, pancreatitis, vasculitis, thromboembolism, burns, or surgery. SIRS was previously defined as two or more abnormalities in temperature, heart rate, respiration, or white blood cell count[3]. However, in practice, its clinical definition and pathophysiology are nonequivocal such that SIRS and early sepsis cannot be readily distinguished. Thus, when SIRS is suspected, it should prompt an evaluation for a septic focus.

Δ Hypoperfusion is defined by hypotension persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L[4]. Refer to the UpToDate topic on the definition of sepsis and SIRS for additional details.

◊ Goal-directed therapy for initial resuscitation includes the following: (a) central venous pressure 8 to 12 mmHg; (b) mean arterial pressure ≥65 mmHg; (c) urine output ≥0.5 mL/kg per hour; and (d) central venous (superior vena cava) oxygen saturation ≥70 percent or mixed venous oxygen saturation ≥65 percent[4]. Refer to the UpToDate topic on evaluation and management of sepsis for additional details.

§ Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection (eg, temperature >38.3 or <36°C, heart rate >90 beats/minute, respiratory rate >20 breaths/minute, altered mental status, leukocytosis, arterial hypotension, arterial hypoxemia)[4]. Refer to the UpToDate topic on the definition of sepsis and SIRS for the full diagnostic criteria for sepsis.

¥ Patients at low risk for serious complications are defined as those who are expected to be neutropenic (absolute neutrophil count [ANC] <500 cells/microL) for ≤7 days and those with no comorbidities or evidence of significant hepatic or renal dysfunction. High-risk patients are defined as those who are expected to be neutropenic (ANC <500 cells/microL) for >7 days; patients with neutropenic fever who have ongoing comorbidities or evidence of significant hepatic or renal dysfunction are also considered to be high risk, regardless of the duration of neutropenia. The Multinational Association for Supportive Care in Cancer (MASCC) risk index can also be used for determining risk. A MASCC score of ≥21 predicts a low risk for medical complications of neutropenic fever syndromes that would require hospitalization and/or prolonged length of hospitalization. A score of <21 predicts patients at high risk for such complications[5]. Refer to the text for more details regarding the definitions of low- and high-risk patients based upon clinical criteria and the MASCC risk score.

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Graphic 57616 Version 10.0

Diagnostic evaluation of patients with fever and neutropenia

Item	Purpose	Comments
Targeted history	Seek sites suspicious for infection	Allows detection of symptoms of infection
Physical exam with emphasis on skin, oral cavity, oropharynx, lungs, abdomen, perianal area*	Detection of sites suspicious for infection; guides selection of cultures and imaging	Pain and/or erythema may point to infection; pus is not found due to lack of neutrophils; chest exam may be unremarkable even with pneumonia; abdominal tenderness may suggest neutropenic enterocolitis; perianal or hemorrhoidal tenderness may point to gram-negative or anaerobic infection
Complete blood count with differential	Defines the depth of neutropenia	The lower the initial neutrophil count, the greater the likelihood of serious infection or bacteremia; daily counts allow prognostication
Creatinine, liver function tests, electrolytes	Defines comorbid conditions	Allows optimal selection and dose of antimicrobial agent(s) and serial monitoring of toxicities
Blood cultures (two sets: one peripheral and one from central venous catheter); antimicrobial susceptibility testing	Detection of bacteremia	Fever may be the only sign of bacteremia; allows adjustment of antibiotic regimen if necessary
Cultures and stains of samples from suspected sites of infection	Detection of infectious etiology	Bacterial and fungal stains can be helpful
Imaging studies (generally recommended only if site is suspected from history or exam)	Detection of infectious site	Computed tomography (CT) scans are generally more useful than plain radiographs; pulmonary infiltrates may be inapparent by plain radiography during deep neutropenia and may become manifest only upon neutrophil recovery; thickened bowel walls are seen by CT scan with neutropenic enterocolitis

* Digital rectal examination is avoided in neutropenic patients.

Graphic 50509 Version 6.0

Contributor Disclosures

Eric Bow, MD Consultant/Advisory Boards: Cidara [Invasive fungal infection]. **John R Wingard, MD** Consultant/Advisory Boards: Ansun [Respiratory virus]; Shire [Antiviral]; Celgene [CAR T]; Merck [Antiviral]; Cidara [Antifungal]; ReViral [Antiviral]. **Carol A Kauffman, MD** Grant/Research/Clinical Trial Support: Laboratoires SMB SA [Antifungal]. Consultant/Advisory Boards: Cidara Therapeutics [Treatment of candidiasis]. **Sheila Bond, MD** Nothing to disclose

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