



Treatment of neutropenic fever syndromes in adults with hematologic malignancies and hematopoietic cell transplant recipients (high-risk patients)

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INTRODUCTION

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 or fungi that translocate across intestinal mucosal surfaces. Patients with profound prolonged neutropenia are at particularly high risk for serious infections; profound prolonged neutropenia is most likely to occur in the pre-engraftment phase of hematopoietic cell transplantation (HCT; particularly allogeneic) and in patients undergoing induction chemotherapy for acute leukemia.

Because neutropenic patients are unable to mount robust inflammatory responses, serious infection can occur with minimal symptoms and signs. In such patients, fever is often the only sign of infection. Infections in neutropenic patients can progress rapidly, leading to hypotension or other life-threatening complications. It is critical to recognize neutropenic fever early and to initiate empiric systemic antibacterial therapy promptly to avoid progression to a sepsis syndrome and possibly death [1,2].

The use of empiric antibacterial and antifungal therapy for high-risk neutropenic adults presenting with fever will be reviewed here. The management of neutropenic fever in cancer

patients at low risk for complications is discussed separately. An overview of neutropenic fever syndromes, the risk assessment of patients with neutropenic fever, and the diagnostic approach to patients presenting with neutropenic fever are presented elsewhere. The use of antimicrobial prophylaxis and colony stimulating factors to prevent infections in HCT recipients and patients with chemotherapy-induced neutropenia is also discussed separately.

- (See ["Treatment and prevention of neutropenic fever syndromes in adult cancer patients at low risk for complications"](#).)
- (See ["Overview of neutropenic fever syndromes"](#).)
- (See ["Risk assessment of adults with chemotherapy-induced neutropenia"](#).)
- (See ["Diagnostic approach to the adult cancer patient with neutropenic fever"](#).)
- (See ["Prophylaxis of infection during chemotherapy-induced neutropenia in high-risk adults"](#).)
- (See ["Prophylaxis of invasive fungal infections in adults with hematologic malignancies"](#).)
- (See ["Prophylaxis of invasive fungal infections in adult hematopoietic cell transplant recipients"](#).)
- (See ["Prevention of infections in hematopoietic cell transplant recipients"](#).)
- (See ["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"](#).)

Neutropenic fever in children is also presented separately. (See ["Fever in children with chemotherapy-induced neutropenia"](#).)

DEFINITIONS

Fever — Fever in neutropenic patients is defined as a single oral temperature of $\geq 38.3^{\circ}\text{C}$ (101°F) or a temperature of $\geq 38.0^{\circ}\text{C}$ (100.4°F) sustained over a one-hour period [1]. The definition of fever and appropriate methods for measuring body temperature are discussed in greater detail separately. (See ["Overview of neutropenic fever syndromes"](#), section on 'Fever' and ["Overview of neutropenic fever syndromes"](#), section on 'Temperature measurement'.)

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, and severe neutropenia is usually defined as an ANC <500 cells/microL or an ANC that is expected to decrease to <500 cells/microL over the next 48 hours [1]. Profound neutropenia is defined as an ANC <100 cells/microL. 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). The risk for bacteremic infection rises as the ANC falls below 100 cells/microL. For the purposes of this discussion, **we are defining severe neutropenia as an ANC <500 cells/microL.**

The ANC can be calculated by multiplying the total white blood cell count by the percentage of polymorphonuclear cells and bands ([calculator 1](#)). (See "[Overview of neutropenic fever syndromes](#)", section on 'Neutropenia' and "[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'.)

RISK OF SERIOUS COMPLICATIONS

The initial clinical evaluation focuses on assessing the risk of serious complications. This risk assessment dictates the approach to therapy, including the need for inpatient admission, intravenous antibiotics, and prolonged hospitalization. The factors that are associated with serious complications are summarized in the table ([table 1](#)) and discussed in greater detail separately. (See "[Overview of neutropenic fever syndromes](#)", section on 'Risk of serious complications' and "[Risk assessment of adults with chemotherapy-induced neutropenia](#)".)

INITIAL ASSESSMENT

In patients presenting with neutropenic fever, a reliable method for obtaining body temperature must be used, and a mechanism for estimating the absolute neutrophil count (ANC) is mandatory. The temperature should be taken using oral or tympanic thermometry. (See "[Overview of neutropenic fever syndromes](#)", section on 'Temperature measurement'.)

Risk of neutropenia — Patients and their caregivers should be instructed by their hematologist or 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. The ANC can be estimated based upon the timing of the febrile episode following the first dose of the current cytotoxic chemotherapy or from a laboratory-

based measurement of the ANC from a complete blood count ([calculator 1](#)). Knowledge that the ANC reaches its nadir of <500 cells/microL at a median of 12 to 14 days from day 1 of chemotherapy can guide the clinician to the correct index of suspicion regarding the likelihood of neutropenia.

Over 70 percent of cancer recipients who develop systemic therapy-related complications present to emergency triage facilities within four to six weeks of systemic anticancer treatment [3]. The use of a sensitive but nonspecific historical indicator, receipt of systemic anticancer therapy within the preceding six weeks, has been advocated for use in emergency triage departments to identify patients who are likely to be neutropenic [4].

Risk of complications — As discussed above, it is crucial to assess the risk of 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.)

Identification of sepsis — Although the signs and symptoms of infection may be significantly muted in neutropenic patients [5-7], an early part of the clinical assessment at triage should include an examination for evidence of a systemic inflammatory response syndrome and a determination of the criteria for sepsis, severe sepsis, or septic shock [4]. (See "[Sepsis syndromes in adults: Epidemiology, definitions, clinical presentation, diagnosis, and prognosis](#)", section on '[Definitions](#)'.)

Patients presenting with evidence of new organ dysfunction (altered mental status, hypotension, or hypoxia) should be managed emergently for severe sepsis. Patients with septic shock should be managed in a critical care hospital environment. (See "[Evaluation and management of suspected sepsis and septic shock in adults](#)".)

Diagnostic evaluation — The diagnostic evaluation of patients presenting with neutropenic fever is summarized in the following table ([table 2](#)) and is discussed in detail separately. (See "[Diagnostic approach to the adult cancer patient with neutropenic fever](#)".)

EMPIRIC THERAPY

General principles — Fever in a neutropenic patient should be considered a medical emergency. Broad-spectrum antibacterials should be given as soon as possible (within 60 minutes of triage) and at full doses, adjusted for renal and/or hepatic function. In addition, the diagnostic evaluation should be obtained quickly. (See "[Diagnostic approach to the adult cancer patient with neutropenic fever](#)".)

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](#)) [1]. The following general principles apply:

- Antibiotics are usually administered empirically but should always include appropriate coverage for suspected or known infections. Even when the pathogen is known, the antibiotic regimen should provide broad-spectrum empiric coverage for the possibility of other pathogens, unlike the treatment strategy adopted in many immunocompetent hosts.
- In high-risk patients, antibiotics should generally be administered intravenously (IV) in a hospital setting.
- Initial antibiotic selection should be guided by the patient's history, allergies, symptoms, signs, recent antibiotic use and culture data, and awareness of the susceptibility patterns of institutional nosocomial pathogens [8].
- Ideally, antibiotics should be bactericidal.
- Clinical response and culture and susceptibility results should be monitored closely, and therapy should be adjusted in a timely fashion in response to this information [9].

Febrile neutropenic patients should be monitored frequently with respect to vital signs (blood pressure, heart rate, respiratory rate, and temperature), performance status (the clinical burden of the neutropenic fever syndrome), and the ability to achieve adequate oral intake in the presence of oral or gastrointestinal mucositis. Temporarily holding administration of systemic chemotherapy should be considered during the management of the sepsis syndrome until the patient stabilizes. Attention to fluid and electrolyte management is important given the dehydrating effects of fever, vomiting, and/or diarrhea. Urine output of >0.5 mL/kg per hour should be maintained.

Afebrile neutropenic patients with new signs or symptoms that are consistent with infection should be evaluated and managed as if they are febrile [1].

Timing of antibiotics — In all febrile neutropenic patients, empiric broad-spectrum antibacterial therapy should be initiated immediately after blood cultures have been obtained and before any other investigations have been completed [4,10]. Antimicrobial therapy should be administered within **60 minutes** of presentation [4,11,12]. Some investigators have argued that initial empiric antimicrobial therapy should be administered within 30 minutes [13]; we

agree that antibiotics should be given as early as possible. This is discussed in greater detail separately. (See ["Overview of neutropenic fever syndromes", section on 'Timing of antibiotics'](#).)

Spectrum of coverage — Although gram-positive bacteria are the most frequent pathogens identified during neutropenic fever episodes, it is important to cover broadly for gram-negative pathogens because of their virulence and association with sepsis [12,14]. Furthermore, gram-negative organisms continue to cause the majority of infections in sites outside of the bloodstream (eg, respiratory tract, biliary tract, gastrointestinal tract, urinary tract, and skin) [15], and a rising number of infections are polymicrobial [12,14]. Clinicians need to be aware of the current microbiology surveillance data from their own institution, which can vary widely from center to center and over time [8,12].

Although anaerobic bacteria are present in abundance in the gastrointestinal tract, it is usually not necessary to include specific anaerobic antibiotic coverage in the initial empiric regimen. Anaerobic bacteremia occurred in only 3.4 percent of episodes in a large series of cancer patients from France [16], and anaerobic bacteria are often part of polymicrobial infections [17,18]. Anaerobic coverage should be included in the regimens of patients with infections that are known or expected to be caused by anaerobes, as discussed below. (See ["Initial regimen"](#) below.)

As the duration of profound neutropenia increases, the risk of invasive fungal infections (eg, candidiasis, invasive aspergillosis) becomes substantial in patients with neutropenic fever. (See ["Overview of neutropenic fever syndromes", section on 'Fungal pathogens'](#) and ["Addition of an antifungal agent"](#) below.)

The epidemiology of infections in febrile neutropenic patients is discussed in greater detail separately. (See ["Overview of neutropenic fever syndromes", section on 'Epidemiology'](#).)

Initial regimen — The choice of antibiotics is driven by multiple factors, including the degree of immunocompromise, prior antibiotic and infection history, local patterns of antibiotic resistance, and whether an agent is bactericidal or not [1,12]. Some drugs, such as beta-lactams, exhibit time-dependent killing. When using beta-lactams, correct dosing intervals should be used to ensure that drug concentrations are greater than the minimal inhibitory concentration for the pathogen. There has been increasing interest in giving prolonged infusions of beta-lactams (either an extended infusion over three or four hours or a continuous infusion) rather than traditional dosing over 30 minutes to optimize pharmacodynamics [19]. Indications for the use of prolonged infusion strategies with beta-lactams are not established, but it is reasonable to give prolonged infusions in patients with neutropenic fever who are

severely ill and/or who have an elevated risk of drug-resistant gram-negative bacilli. (See ["Prolonged infusions of beta-lactam antibiotics"](#).)

Other antibiotics, such as aminoglycosides and fluoroquinolones, exhibit concentration-dependent killing and are important in the treatment of gram-negative sepsis.

Our approach — The Infectious Diseases Society of America (IDSA) recommends the following approach for the initial therapy of high-risk neutropenic patients with fever ([algorithm 1](#)) [1]; we agree with this approach:

- Initiation of monotherapy with an antipseudomonal beta-lactam agent, such as [cefepime](#), [meropenem](#), [imipenem](#), or [piperacillin-tazobactam](#). [Ceftazidime](#) monotherapy has also been shown to be effective and continues to be used at some cancer centers with low rates of resistance. However, we generally avoid ceftazidime monotherapy because of rising resistance rates among gram-negative bacteria and its limited activity against gram-positive bacteria, such as streptococci, compared with newer alternatives. Ceftazidime monotherapy should not be used when there is concern for a gram-positive infection, such as an infection caused by viridans group streptococci in patients with severe mucositis. The dosing of these agents for patients with normal renal function using traditional dosing (ie, over 30 minutes) are:
 - [Cefepime](#) – 2 g IV every eight hours
 - [Meropenem](#) – 1 g IV every eight hours
 - [Imipenem](#) – 500 mg IV every six hours
 - [Piperacillin-tazobactam](#) – 4.5 g IV every six to eight hours; if there is significant concern for *Pseudomonas* infection (particularly in those who are severely ill or were not receiving fluoroquinolone prophylaxis at the time of onset of illness), 4.5 g IV every six hours should be given
 - [Ceftazidime](#) – 2 g IV every eight hours

As noted above, prolonged infusions of beta-lactams can be used instead of traditional dosing when optimization of pharmacodynamics is thought to be important.

- Other antibiotics (eg, aminoglycosides, fluoroquinolones, and/or [vancomycin](#)) may be added to the initial regimen in patients with complicated presentations (eg, hypotension and/or mental status changes), focal findings (eg, pneumonia or cellulitis), or if antimicrobial resistance is suspected or proven.

- **Vancomycin** (or other agents that target gram-positive cocci) is **not** recommended as a standard part of the initial regimen but should be added in certain patients, such as those with suspected catheter-related infection, skin or soft tissue infection, pneumonia, or hemodynamic instability. (See '[Addition of gram-positive coverage](#)' below.)
- Modifications to the initial regimen should be considered for patients at risk for infection with antibiotic-resistant organisms, patients who are clinically unstable, and patients with positive blood cultures that are suggestive of a resistant infection. Risk factors for infections caused by resistant bacteria include previous infection or colonization by the organism and/or treatment in a hospital with high rates of resistance. (See '[Modifications to the regimen](#)' below and '[Antibiotic resistance](#)' below.)

In addition, we suggest that anaerobic coverage be included if there is evidence of necrotizing mucositis, sinusitis, periodontal cellulitis, perirectal cellulitis, intra-abdominal infection (including neutropenic enterocolitis [typhlitis]), pelvic infection, or anaerobic bacteremia. (See "[Neutropenic enterocolitis \(typhlitis\)](#)" and "[Clinical presentation and risk factors for chemotherapy-associated diarrhea, constipation, and intestinal perforation](#)".)

Comparisons of regimens

Monotherapy — Monotherapy with a beta-lactam agent with activity against *Pseudomonas aeruginosa* (eg, [cefepime](#), [meropenem](#), [imipenem](#), [piperacillin-tazobactam](#), or [ceftazidime](#)) is frequently employed; clinical trials with ceftazidime, imipenem, or meropenem have demonstrated equivalent outcomes compared with two-drug regimens [20-23]. In addition, fewer adverse events have generally been seen with monotherapy regimens compared with combination regimens [24]. The majority of the regimens evaluated provided coverage targeted at gram-negative bacilli, especially *P. aeruginosa*.

Single drugs have also been compared with each other in various clinical trials of empiric therapy for patients with neutropenic fever, as illustrated below:

- In a multicenter randomized trial, treatment with [meropenem](#) was compared with [ceftazidime](#) in 411 patients and the outcomes were similar for clinically defined and microbiologically defined infections [25].
- Another trial assessed [cefepime](#) versus [imipenem](#) in 251 patients [26]. In an intent-to-treat analysis, the response to treatment in the two groups was comparable (75 versus 68 percent, respectively) as was the side-effect profile.

- A multicenter open-label randomized trial compared the efficacy and safety of [piperacillin-tazobactam](#) and [cefepime](#) in 528 patients [27]. On multivariate analysis, treatment with piperacillin-tazobactam was associated with greater treatment success (odds ratio 1.65, 95% CI 1.04-2.64).
- A meta-analysis of clinical trials showed increased mortality among patients who received [cefepime](#) compared with other beta-lactam antibiotics, particularly in those with neutropenic fever; both groups included patients who received either monotherapy or combination therapy of a beta-lactam plus a non-beta-lactam antibiotic [28]. However, in a subsequent meta-analysis performed by the US Food and Drug Administration (FDA), which included 50 more trials than the original meta-analysis as well as patient-specific information, there was no difference in mortality between patients who received cefepime and patients who received other antibiotics [29,30]. Accordingly, the IDSA guidelines continue to recommend cefepime as a suitable option [1].

One concern about monotherapy is the possibility that increasing rates of 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 [31]. It is therefore important to maintain vigilance for the emergence of antibiotic resistance locally that may necessitate a change in antibiotic practices. (See '[Antibiotic resistance](#)' below.)

Combination therapy — Numerous combination antibiotic regimens have been studied as initial empiric therapy in neutropenic fever, but none has been shown to be clearly superior to others or to monotherapy [32,33]. One approach is to use an extended-spectrum beta-lactam (eg, [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 empiric therapy of neutropenic fever demonstrated similar overall efficacy for clinical cure and all-cause mortality [33]. Double beta-lactams are usually avoided because of overlapping toxicities. In settings characterized by a high prevalence of multidrug-resistant gram-negative bacilli, initial empirical antibacterial therapy with [piperacillin-tazobactam](#) plus [tigecycline](#) may have some advantages over the single agent for documented neutropenic fever syndromes [34].

Penicillin-allergic patients — Many patients with a history of allergy to penicillin tolerate cephalosporins [1] (see "[Allergy evaluation for immediate penicillin allergy: Skin test-based diagnostic strategies and cross-reactivity with other beta-lactam antibiotics](#)"). However, those with a history of an immediate-type hypersensitivity reaction (eg, hives and/or bronchospasm)

should not receive beta-lactams or carbapenems. Alternative empiric regimens for such patients include [aztreonam](#) plus [vancomycin](#) **or** [ciprofloxacin](#) plus [clindamycin](#) [1]. Of these regimens, we prefer aztreonam plus vancomycin out of concern for increasing the risk of *Clostridioides difficile* infection in those requiring clindamycin for an extended period. In general, fluoroquinolones should not be used in patients who have received them recently (including those receiving a fluoroquinolone for neutropenic prophylaxis). The decision of which alternative regimen to use in penicillin-allergic patients should be made based upon the susceptibility patterns of bacteria (especially gram-negative bacilli) at the individual institution as well as the patient's previous microbiologic data.

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 [35-38]. A meta-analysis of 14 randomized trials found that addition of gram-positive antibiotic coverage to standard empiric therapy did not reduce all-cause mortality in patients with cancer and neutropenic fever [38].

Even in febrile neutropenic patients with skin and soft tissue infections who had a higher incidence of proven gram-positive bacteremia compared with patients with other infections (31 versus 17 percent), the addition of empiric [vancomycin](#) did not improve outcomes and was associated with increased toxicity [39]. The risk of promoting resistance among enterococci and *Staphylococcus aureus* is an important reason to avoid empiric vancomycin use [1].

[Vancomycin](#) (or other agents that target gram-positive cocci) is **not** recommended as a standard part of the initial regimen, but gram-positive coverage should be added in patients with any of the following findings [1]:

- Hemodynamic instability or other signs of severe sepsis
- Pneumonia
- Positive blood cultures for gram-positive bacteria while awaiting speciation and susceptibility results
- Suspected central venous catheter (CVC)-related infection (eg, chills or rigors during infusion through a CVC and/or cellulitis around the catheter entry site)
- Skin or soft tissue infection
- Severe mucositis in patients who were receiving prophylaxis with a fluoroquinolone lacking activity against streptococci and in whom [ceftazidime](#) is being used as empiric therapy. Addition of gram-positive coverage is recommended in this situation because of

the increased risk of *viridans* group streptococcal infections, which can result in sepsis and the acute respiratory distress syndrome [1,40-43].

Empiric gram-positive coverage is particularly important for patients who are colonized with methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci (VRE), or penicillin- or ceftriaxone-resistant streptococci who become hemodynamically unstable or develop bacteremia with gram-positive cocci.

The combination of [vancomycin](#) and [piperacillin-tazobactam](#) has been associated with acute kidney injury. In patients who require vancomycin and an antipseudomonal beta-lactam, a beta-lactam other than piperacillin-tazobactam can be used (eg, [cefepime](#)). If vancomycin is used with piperacillin-tazobactam, renal function should be monitored carefully and the regimen should be adjusted to reduce further nephrotoxicity if acute kidney injury develops. (See "[Vancomycin: Parenteral dosing, monitoring, and adverse effects in adults](#)", section on 'Acute kidney injury'.)

A multicenter randomized trial of 611 febrile neutropenic patients compared the safety and efficacy of [linezolid](#) and [vancomycin](#) [44]. 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 with [linezolid](#) and [vancomycin](#) (87 versus 85 percent, respectively).
- Mortality rates at 16 days after completion of therapy were similar (17 of 304 patients who received [linezolid](#) [6 percent] and 23 of 301 [8 percent] who received [vancomycin](#)).
- Drug-related adverse events occurred more frequently in the [vancomycin](#) group (24 versus 17 percent for [linezolid](#)).
- In patients with documented gram-positive infections, those who received [linezolid](#) defervesced more quickly than those who received [vancomycin](#) (5.9 versus 9.1 days); there was no difference in time to defervescence among patients without documented infections.

[Daptomycin](#) is another alternative to [vancomycin](#), but it has been less well studied and should **not** be used for pulmonary infections because it is inactivated by surfactant and therefore does not achieve sufficiently high concentrations in the respiratory tract. (See "[Daptomycin: An overview](#)".)

Modifications to the regimen — Modifications to the antimicrobial regimen during the course of neutropenic fever can be made based upon the following principles [1]:

- The initial treatment regimen should be modified based upon clinical and microbiologic data.
- Unexplained persistent fever in a patient who is otherwise stable rarely necessitates an empiric adjustment to the initial antibacterial regimen. However, if an infection is identified, the regimen should be adjusted accordingly.
- Documented infections (based on clinical findings and/or microbiologic data) should be treated with antibiotics that are appropriate for the site and susceptibility patterns of organisms that are isolated.
- If [vancomycin](#) or other gram-positive coverage was started initially, it may be stopped after two to three days if there is no evidence of a gram-positive infection. Vancomycin overuse has been associated with the development of resistance (eg, vancomycin-resistant *Enterococcus* spp).
- Patients who are or become hemodynamically unstable after initial doses of a standard antimicrobial regimen for neutropenic fever should have their regimen broadened to include coverage for resistant gram-negative, gram-positive, and anaerobic bacteria as well as fungi. (See '[Antibiotic resistance](#)' below and '[Addition of an antifungal agent](#)' below.)
- Empiric antifungal coverage should be considered in high-risk patients who have persistent fever after four to seven days of a broad-spectrum antibacterial regimen and no identified source of fever. (See '[Addition of an antifungal agent](#)' below.)
- Oral ulcerations may be due to herpes simplex virus or *Candida* spp. Thus, addition of [acyclovir](#) and/or [fluconazole](#) may be warranted if these findings are present. (See "[Oropharyngeal candidiasis in adults](#)".)
- In patients with diarrhea, if there are abdominal signs, empiric therapy of *C. difficile* can be instituted while assays are pending. (See "[Clostridioides difficile infection in adults: Treatment and prevention](#)".)

Persistent fever — The median time to defervescence following the initiation of empiric antibiotics in patients with hematologic malignancies, including hematopoietic cell transplant (HCT) recipients, is five days, in contrast with only two days for patients with solid tumors [1]. As stated above, modification of the initial antibacterial regimen is **not** needed for persistent fever alone. However, patients who remain febrile after the initiation of empiric antibiotics should be

re-evaluated for possible infectious sources. (See "[Diagnostic approach to the adult cancer patient with neutropenic fever](#)".)

Management algorithms have been developed for the reassessment of neutropenic patients with persistent fever after two to four days ([algorithm 2](#)) and after four or more days ([algorithm 3](#)) [1]. Key factors in the management of patients with persistent fever include whether the patient is clinically stable, whether there is an identified site of infection, and when the patient is expected to recover from neutropenia. Consideration should be given to the addition of empiric antifungal therapy, as described below. (See '[Addition of an antifungal agent](#)' below.)

Antibiotic resistance — The increasing frequency of antibiotic-resistant organisms is a major concern [45,46]. Depending upon local epidemiology, consideration of the risk of antibiotic-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. The increasing frequency of multidrug-resistant gram-negative bacterial infections is forcing the renewed use of older agents that have been used infrequently in febrile neutropenic cancer patients, such as [colistin](#) (colistimethate) and [fosfomycin](#), and newer agents, such as [tigecycline](#) [47]. Similarly, beta-lactam- or glycopeptide-resistant gram-positive organisms have forced the use of lipopeptides ([daptomycin](#)), oxazolidinones ([linezolid](#)), and glycylcyclines (tigecycline).

The patient's risk for the following resistant organisms should be considered when choosing an empiric regimen:

- Among gram-positive organisms, pathogens with acquired resistance include coagulase-negative staphylococci, MRSA, VRE, and penicillin- and ceftriaxone-resistant *Streptococcus pneumoniae* and other streptococci.
- Gram-positive organisms that have intrinsic resistance to [vancomycin](#) (*Leuconostoc*, [Lactobacillus](#), and *Pediococcus* spp).
- Multidrug-resistant gram-negative bacilli, such as *P. aeruginosa*, *Escherichia coli*, and *Citrobacter*, *Acinetobacter*, and *Stenotrophomonas* spp [9]. The use of fluoroquinolones for prophylaxis has contributed to the emergence of antibiotic resistance.
- The presence of extended-spectrum beta-lactamases (ESBL), plasmid-mediated AmpC-type beta-lactamases, and carbapenemase-producing bacteria (eg, *Klebsiella pneumoniae* carbapenemase [KPC]) can severely limit treatment options [12,48,49].

Risk factors for infections with resistant bacteria include previous infection or colonization by the organism, recent use of antibacterial agents (eg, for prophylaxis), and treatment in a hospital with high rates of resistance [1]. It is important to be aware of institutional resistance patterns since a variety of nosocomial outbreaks involving cancer patients have been reported. Some centers have reported an increased incidence of resistant pathogens with the routine use of prophylactic antibiotics [50-52]. 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 unneeded empiric therapies (eg, [vancomycin](#)) when cultures remain negative, and initiation of antibiotic stewardship programs [12]. (See '[Addition of gram-positive coverage](#)' above.)

The following antibiotics can be used when resistant infections are suspected [1]:

- MRSA – [Vancomycin](#), [linezolid](#), or [daptomycin](#); daptomycin should be avoided in patients with pneumonia because it does not achieve sufficiently high concentrations in the respiratory tract. (See "[Methicillin-resistant Staphylococcus aureus \(MRSA\) in adults: Treatment of bacteremia](#)" and "[Methicillin-resistant Staphylococcus aureus \(MRSA\) in adults: Treatment of skin and soft tissue infections](#)" and "[Treatment of hospital-acquired and ventilator-associated pneumonia in adults](#)", section on 'Risk factors for MRSA'.)
- VRE – [Linezolid](#) or [daptomycin](#). (See "[Treatment of enterococcal infections](#)".)
- ESBL-producing gram-negative bacilli – A carbapenem (eg, [imipenem](#), [meropenem](#)). (See "[Extended-spectrum beta-lactamases](#)", section on 'Treatment options' and "[Gram-negative bacillary bacteremia in adults](#)", section on 'Extended-spectrum beta-lactamases'.)
- Carbapenemase-producing bacteria, including *K. pneumoniae* carbapenemase – [Colistin](#) or [tigecycline](#). (See "[Carbapenem-resistant E. coli, K. pneumoniae, and other Enterobacterales \(CRE\)](#)", section on 'Approach to treatment' and "[Gram-negative bacillary bacteremia in adults](#)", section on 'Carbapenem resistance'.)

In an open-label trial that included 390 high-risk patients with hematologic malignancies, combination therapy for neutropenic fever with [piperacillin-tazobactam](#) plus [tigecycline](#) was associated with significantly higher success rates compared with piperacillin-tazobactam alone (68 versus 44 percent), especially in those with bacteremia due to *E. coli* or *Staphylococcus epidermidis* [34]. Mortality rates were similar in both groups, but the study was not powered to detect a difference in this outcome. Among *E. coli* bloodstream isolates, 33 percent were

resistant to piperacillin-tazobactam and 7 percent were resistant to tigecycline. Of *Klebsiella* spp bloodstream isolates, 36 percent were resistant to piperacillin-tazobactam and 10 percent were resistant to tigecycline. In our opinion, tigecycline should only be used for empiric therapy of neutropenic fever in centers with a high rate of multidrug-resistant infections caused by *E. coli* or *Klebsiella*.

Bacteremia due to antibiotic-resistant bacteria such as ESBL-producing *E. coli* or *K. pneumoniae* in neutropenic cancer patients has been associated with significant delays in the initiation of effective therapy in up to one-half of cases and 30-day all-cause mortality rates as high as 45 percent (versus 14 percent in patients with bacteremia caused by non-ESBL-producing bacteria) [53].

Addition of an antifungal agent

Indications — An empiric antifungal agent should be added after four to seven days in high-risk neutropenic patients who are expected to have a total duration of neutropenia >7 days who have persistent or recurrent fever and in whom reassessment does not yield a cause ([algorithm 3](#)) [1]. The rationale for this approach is that undiagnosed fungal infection was found in early studies in many patients who died during prolonged neutropenia [54,55]. The incidence of fungal infection (especially those caused by *Candida* or *Aspergillus* spp) rises after patients have experienced more than seven days of persistent neutropenic fever [54-56].

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 "[Management of candidemia and invasive candidiasis in adults](#)" and "[Treatment and prevention of invasive aspergillosis](#)".)

An ongoing question is whether all high-risk neutropenic patients with persistent fever need to receive empiric antifungal therapy, since fungal infection is not documented in most patients. The following observations provide limited support for this practice:

- In an autopsy study of patients who died after prolonged neutropenic fever between 1966 and 1975, 69 percent of patients had evidence of systemic fungal infection [56]. It should be noted that over one-half of the patients in this early series had *Candida* infections, which may have been effectively prevented with antifungal prophylaxis strategies. For example, in one trial, fungal infections were documented in only 1 percent of persistent fevers in patients receiving [fluconazole](#) prophylaxis [57].
- Resolution of fever occurs in approximately 40 to 50 percent of patients given antifungal therapy [55,56,58,59]. However, this does not prove that the patient had an occult fungal

infection. Since slow responses to empiric antibacterial therapy are frequent in high-risk patients, the defervescence noted in temporal association with antifungal therapy may be explained by antibacterial therapy.

Choice of drug — The choice of agent for empiric antifungal therapy depends upon which fungi are most likely to be causing infection as well as the toxicity profiles and cost ([algorithm 3](#)) [1]. In patients who have not been receiving antifungal prophylaxis, *Candida* spp are the most likely cause of invasive fungal infection. In patients receiving [fluconazole](#) prophylaxis, fluconazole-resistant *Candida* spp (eg, *C. glabrata* and *C. krusei*) and invasive mold infections, particularly *Aspergillus* spp, are the most likely causes.

The 2010 IDSA guidelines for empiric antifungal therapy recommend [amphotericin B deoxycholate](#), a lipid formulation of amphotericin B, [caspofungin](#), [voriconazole](#), or [itraconazole](#) as suitable options for empiric antifungal therapy in neutropenic patients [1]. The evidence to support the use of each of these agents is presented below. (See '[Studies](#)' below.)

We favor the following approach:

- For persistently febrile patients who have not been receiving antifungal prophylaxis and who have no obvious site of infection, such as pulmonary nodules, we favor [caspofungin](#) (or another echinocandin) since *Candida* spp is a likely cause in such patients and the echinocandins provide excellent coverage for *Candida* spp and are well tolerated.
- For persistently febrile patients with pulmonary nodules or nodular pulmonary infiltrates, invasive mold infection should be strongly suspected and treated. Prompt assessment frequently requires bronchoscopy with bronchoalveolar lavage with cultures, stains, and *Aspergillus* galactomannan antigen testing to distinguish bacterial from mold pathogens, while simultaneously initiating antibacterial and antimold therapy until the specific etiology is established [60]. (See "[Diagnosis of invasive aspergillosis](#)", section on '[Approach to diagnosis](#)'.)
- Azoles with antimold activity ([voriconazole](#), [posaconazole](#), or [isavuconazole](#)) [61,62] or a lipid formulation of amphotericin B are preferred in patients with pulmonary findings suggestive of an invasive mold infection due to higher failure rates with [caspofungin](#) in preventing and treating invasive aspergillosis, which is the most common cause of mold infections [63]. Current data are insufficient to conclusively determine whether a mold-active azole or a lipid formulation of amphotericin B is optimal; the choice of the initial antifungal agent may vary based on an institution's experience (ie, epidemiology and susceptibility patterns) and patient risks for specific mold infections (eg, *Aspergillus* versus the agents of mucormycosis). The efficacy of all three mold-active azoles is comparable for

the treatment of suspected or documented aspergillosis. However, if mucormycosis is suspected, posaconazole, isavuconazole, or an amphotericin B formulation should be given since voriconazole has no activity against the agents of mucormycosis. It is important to note that at most centers, aspergillosis accounts for the majority of invasive fungal infections in neutropenic patients. (See "[Prophylaxis of invasive fungal infections in adults with hematologic malignancies](#)", section on 'Epidemiology' and "[Prophylaxis of invasive fungal infections in adult hematopoietic cell transplant recipients](#)", section on 'Epidemiology' and "[Epidemiology and clinical manifestations of invasive aspergillosis](#)" and "[Treatment and prevention of invasive aspergillosis](#)" and "[Mucormycosis \(zygomycosis\)](#)".)

- For persistently febrile patients who have been receiving antimold prophylaxis, a different class of antifungal agent with activity against molds should be used for empiric therapy. For example, if [voriconazole](#) or [posaconazole](#) has been used for prophylaxis, an amphotericin B formulation should be used. We favor a lipid formulation of amphotericin B rather than [amphotericin B deoxycholate](#) in order to minimize toxicity. In addition, for suspected breakthrough mold infection in patients receiving mold-active azoles, a prompt and aggressive approach to establish a specific diagnosis is recommended [60]. Serum trough levels of the prophylactic azole should be obtained if feasible. If a breakthrough mold infection is diagnosed, antifungal susceptibility testing should be considered. (See "[Antifungal susceptibility testing](#)".)

It is also important to remember that [caspofungin](#) and other echinocandins are not active against *Cryptococcus* spp, *Trichosporon* spp, and filamentous molds other than *Aspergillus* spp, such as *Fusarium* spp. In addition, some yeasts can demonstrate relative resistance to these drugs (*Candida parapsilosis*, *Candida rugosa*, *Candida guilliermondii*, and non-candidal yeasts). Failure of caspofungin to prevent aspergillosis has also been reported, even though it has in vitro activity against *Aspergillus* spp [64]. Moreover, the echinocandins are not active against the endemic fungi (*Histoplasma*, *Blastomyces*, *Coccidioides* spp). (See "[Cryptococcus neoformans infection outside the central nervous system](#)" and "[Cryptococcus neoformans: Treatment of meningoencephalitis and disseminated infection in patients without HIV](#)" and "[Infections due to Trichosporon species and Blastoschizomyces capitatus \(Saprochaete capitata\)](#)" and "[Diagnosis and treatment of disseminated histoplasmosis in patients without HIV](#)" and "[Treatment and prevention of Fusarium infection](#)".)

Dosing — The dosing of the various antifungal agents recommended above is as follows:

- [Caspofungin](#) – Loading dose of 70 mg IV on day 1, then 50 mg IV once daily
- [Micafungin](#) – 100 mg IV daily

- **Anidulafungin** – Loading dose of 200 mg on day 1, followed by 100 mg once daily
- **Voriconazole** – Loading dose of 6 mg/kg IV every 12 hours on day 1, followed by 4 mg/kg IV every 12 hours
- **Isavuconazole** – 200 mg (equivalent to isavuconazonium sulfate 372 mg) IV every 8 hours on days 1 and 2, then 200 mg once daily from day 3 onwards
- **Posaconazole** – 300 mg IV or PO BID on day 1, then 300 mg daily thereafter
- **Amphotericin B lipid complex** – 5 mg/kg IV once daily
- **Liposomal amphotericin B** – 3 to 5 mg/kg IV once daily

Studies — The following observations have been made about each of the agents used for empiric antifungal therapy.

Amphotericin B formulations — **Amphotericin B deoxycholate** has historically been the most common agent given. In a randomized trial of patients with persistent neutropenic fever, **liposomal amphotericin B** was compared with amphotericin B deoxycholate using a composite of five endpoints: survival, resolution of fever during neutropenia, resolution of pre-existing fungal infection, prevention of breakthrough fungal infection, and absence of premature discontinuation of the drug because of toxicity or lack of efficacy [65]. 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. The lipid formulations of amphotericin B have replaced amphotericin B deoxycholate in most centers due to toxicity considerations, but they are more costly. Amphotericin B deoxycholate should be avoided in patients with antecedent renal disease and in those receiving other nephrotoxic drugs. Today, the lipid formulations of amphotericin B have largely replaced amphotericin B deoxycholate due to favorable toxicity profiles.

Echinocandins — A randomized trial compared the echinocandin **caspofungin** to **liposomal amphotericin B** in 1095 patients with persistent neutropenic fever despite four days of empiric antibiotic therapy [66]. The overall success rates (34 and 34 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** than liposomal amphotericin (52 versus 26 percent). Caspofungin was also associated with a significantly higher rate of survival seven days after the completion of therapy (93 versus 89 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 (5 versus 8 percent).

[Micafungin](#), [anidulafungin](#), and [rezafungin](#) are other echinocandins, but they have not been adequately studied or approved by the FDA for patients with neutropenic fever [67,68]. Micafungin appeared to be effective in small studies in patients with neutropenia [69,70]. These agents can be used as alternatives to [caspofungin](#) when caspofungin is not available, since the spectrum and antifungal activity of all three agents is similar. (See "[Pharmacology of echinocandins and other glucan synthesis inhibitors](#)" and "[Management of candidemia and invasive candidiasis in adults](#)".)

Voriconazole — An international open-label randomized trial compared [liposomal amphotericin B](#) to [voriconazole](#) in 837 neutropenic patients with persistent fever [71]. Mortality was similar in both groups. There was a trend toward a better response with liposomal amphotericin B compared with voriconazole in four of five composite endpoints, including overall response (31 versus 26 percent), but voriconazole was associated with significantly fewer documented breakthrough fungal infections (2 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 [72]. More patients had [voriconazole](#) stopped for perceived lack of efficacy (ongoing fevers), although fevers persisted equally in the [liposomal amphotericin B](#) group. The FDA reviewed the results of the trial along with additional information from the sponsor and recommended not to approve a licensed indication for voriconazole for empiric antifungal treatment, since voriconazole did not fulfill the criterion for noninferiority compared with liposomal amphotericin B [64,73]. 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.

Nevertheless, the IDSA guidelines recommend [voriconazole](#) as an option for empiric antifungal therapy due to its proven efficacy against *Candida* and *Aspergillus* spp infections, the chief fungal pathogens in patients with neutropenic fever, and the lower risk of serious toxicity compared with amphotericin B formulations [1].

Other azoles

- [Posaconazole](#) – Posaconazole is a broad-spectrum triazole that has been approved by the FDA for the prophylaxis of fungal infections in neutropenic patients and for the treatment

of mucocutaneous candidiasis. It has in vitro activity against yeasts and molds (such as *Aspergillus* spp and the Mucorales). Posaconazole was found to be noninferior to [voriconazole](#) in the treatment of possible, probable, or proven invasive aspergillosis [61], but it has not been studied for the empiric treatment of invasive fungal infections in neutropenic patients or for the treatment of established mold infections. (See "[Prophylaxis of invasive fungal infections in adults with hematologic malignancies](#)" and "[Prophylaxis of invasive fungal infections in adult hematopoietic cell transplant recipients](#)" and "[Treatment and prevention of invasive aspergillosis](#)", section on 'Posaconazole'.)

- [Isavuconazole](#) (isavuconazonium) – Isavuconazonium is the prodrug of isavuconazole, a broad-spectrum triazole that has been approved by the FDA for the treatment of invasive aspergillosis and invasive mucormycosis in adults. Isavuconazole was found to be noninferior to [voriconazole](#) in the treatment of possible, probable, or proven invasive aspergillosis [62]. However, isavuconazole failed to demonstrate noninferiority to [caspofungin](#) in the initial treatment of candidemia and invasive candidiasis in a randomized-controlled trial [74]. Successful overall response was observed in 60.3 and 71.1 percent among isavuconazole and caspofungin recipients, respectively. Neutropenia represented only 11 percent of the study population; accordingly those results may not be applicable to the persistently febrile neutropenic patient or neutropenic patient with documented invasive candidiasis [74]. (See "[Management of candidemia and invasive candidiasis in adults](#)".)
- [Itraconazole](#) – A randomized trial compared intravenous followed by oral itraconazole with [amphotericin B deoxycholate](#) for up to 28 days as empiric therapy in 384 febrile neutropenic patients [75]. 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 for the itraconazole and amphotericin groups, respectively. Five breakthrough fungal infections were observed in each group.

Despite its efficacy, we do not recommend [itraconazole](#) for patients with neutropenic fever because it has several important drawbacks. It should not be used in patients with an estimated creatinine clearance below 30 mL/minute, and appropriate dosing in hepatic failure has not been well characterized. Itraconazole has negative inotropic properties and can induce or exacerbate congestive heart failure. The IV formulation of itraconazole is no longer available in the United States, and oral formulations have variable bioavailability. It also has a number of important drug interactions, most notably with [cyclosporine](#),

quinidine, and HMG-CoA reductase inhibitors ("statins"). (See "[Pharmacology of azoles](#)", [section on 'Drug interactions'](#).)

- **Fluconazole** – Fluconazole is generally not recommended for empiric antifungal therapy because of its lack of activity against molds, a major concern in patients with hematologic malignancies and those undergoing HCT.

Pre-emptive antifungal therapy — An alternative to empiric antifungal therapy is pre-emptive therapy (or biomarker-driven therapy) [1,60]; this involves serial screening of high-risk patients for markers of fungal colonization and/or infection in an attempt to prevent invasive infection. Such markers include laboratory tests (eg, *Aspergillus* galactomannan antigen, beta-D-glucan assay) and imaging tests (high-resolution chest computed tomography). If one of these markers suggests a fungal infection, antifungal therapy is started. This approach is best suited for patients receiving prophylaxis with an antiyeast agent, such as **fluconazole**, where the concern is mainly mold pathogens and one is considering broadening the coverage to include an antimold agent.

A systematic review of seven randomized trials comparing pre-emptive versus empiric antifungal treatment in febrile patients with cancer found no difference in all-cause mortality or mortality caused by fungal infection [76]. However, the certainty of those findings was low and the studied patient population was broad, including patients with solid tumors, hematologic malignancies, and HCT recipients. Thus, it is not clear that these findings are generalizable. In a subsequent randomized trial of 549 patients with AML or MDS undergoing induction chemotherapy or allogeneic HCT, the incidence of proven or probable fungal infection (7.7 versus 6.6 percent) and overall survival (96.7 versus 93.1 percent) were similar when comparing empiric and pre-emptive **caspofungin** therapy [77]. Empiric caspofungin was given for new or persistent fever while receiving broad-spectrum antibiotics; pre-emptive caspofungin was given to those with concern for fungal infection (ie, galactomannan ODI >0.5, pulmonary infiltrates on chest imaging, dense well-consolidated lesions on chest CT, or recovery of *Aspergillus* spp. from sputum). While these results suggest that use of empiric antifungal therapy can be safely reduced in high-risk neutropenic patients, the diagnostics used in this study may not be available in all settings nor adequately predictive of fungal infection. In addition, all patients were receiving **fluconazole** prophylaxis at baseline, which is not routine practice at all centers. Use of fluconazole or azoles with antimold activity for prophylaxis also varies among centers.

Thus, further study is needed to determine in which patient population pre-emptive antifungal therapy is both safe and effective.

The prevention of aspergillosis, one of the most common fungal infections in neutropenic patients, is discussed separately. (See ["Treatment and prevention of invasive aspergillosis", section on 'Pre-emptive therapy'](#).)

Duration — If an infectious source of fever is identified, antibiotics should be continued for at least the standard duration indicated for the specific infection (eg, 14 days for *E. coli* bacteremia); antibiotics should also continue at least until the absolute neutrophil count (ANC) is ≥ 500 cells/microL or longer if clinically indicated [1].

When no source is identified and cultures are negative, the timing of discontinuation of antibiotics is usually dependent on resolution of fever and clear evidence of bone marrow recovery. If the patient has been afebrile for at least two days and the ANC is ≥ 500 cells/microL and is showing a consistent increasing trend, we generally stop antibiotics; this approach is in accordance with the Infectious Diseases Society of America guidelines [1]. There has been increased interest in assessing the safety of discontinuing antibiotics before recovery from neutropenia in selected patients whose fever has resolved and in whom no source of infection is found. Several studies provide increasing support for this type of approach with varying lengths of time remaining afebrile, generally three to seven days [78-81]. Such early discontinuation is endorsed by the European Conference on Infections in Leukemia [82]. We believe that early discontinuation of antibiotics can be tried as long as patients can be monitored closely. An alternative approach in patients who remain neutropenic involves continuing antibiotics until an appropriate treatment course has been completed and all signs and symptoms of infection have resolved and then switching to oral fluoroquinolone prophylaxis until marrow recovery has occurred; however, this approach requires more study [1,83].

In patients with an identifiable cause of fever (eg, a urinary tract infection caused by *E. coli*) who have had steady clinical improvement but who require continued antibiotic therapy following the resolution of neutropenia to complete the course of therapy, a switch from IV antibiotic therapy to appropriate oral agents can be considered.

Antibacterial use in the setting of stem cell allografting may impact survival independent from the intended antibacterial effect. Broad-spectrum antibacterial regimens based upon carbapenems or antipseudomonal penicillins through their suppressive effects on the gut microbiome may enhance the risk for graft-versus-host-related complications, including mortality [84-86]. These observations argue for judicious use of antibacterial therapy.

CATHETER REMOVAL

Central venous catheter (CVC)-related infections are common in patients with neutropenic fever. If blood cultures drawn from the CVC become positive at least 120 minutes before peripheral blood cultures drawn at the same time, then the CVC is likely to be the source of the bacteremia [1]. In addition to antibiotics, CVC removal is recommended for patients with catheter-related bloodstream infections in which any of the following organisms is implicated [1]:

- *S. aureus*
- *P. aeruginosa*
- *Candida* species (see "[Management of candidemia and invasive candidiasis in adults](#)")
- Other fungi
- Rapidly growing nontuberculous mycobacteria

This recommendation is based upon observational studies showing improved clearance of infection and, in some cases, a mortality benefit among patients with *S. aureus*, *P. aeruginosa*, or *Candida* spp bloodstream infections in whom the CVC was removed [87-92]. In a study of cancer patients with bacteremia caused by rapidly growing mycobacteria, CVC removal was associated with a significantly reduced rate of relapse of bacteremia [93]. There are no studies that have demonstrated the benefit of CVC removal in patients with CVC-related bloodstream infections caused by fungi other than *Candida* spp, but CVC removal is generally recommended in such patients based upon the severity of these infections and the biologic plausibility of the potential benefit of this intervention.

Antibiotics should be administered for a minimum of 14 days following catheter removal **and** clearance of blood cultures.

Catheter removal is also recommended for tunnel infection, port pocket infection, septic thrombosis, endocarditis, sepsis with hemodynamic instability, and bloodstream infection that persists despite ≥72 hours of therapy with appropriate antibiotics, even when pathogens other than those described above are isolated [1].

A prolonged duration of treatment of four to six weeks is recommended for patients with complicated CVC-associated infections, such as those with deep tissue infection, endocarditis, septic thrombosis, or persistent bacteremia or fungemia occurring >72 hours following catheter removal in a patient receiving appropriate antimicrobial therapy [1]. The evidence to support the need for an extended duration of therapy is strongest for *S. aureus*, but this approach is also suggested for complicated infections caused by other pathogens.

For CVC-associated bacteremia caused by coagulase-negative staphylococci, the CVC may be retained; in this setting, patients are treated with systemic antibiotics with or without antibiotic lock therapy [1].

Although the Infectious Diseases Society of America guidelines recommend CVC removal in patients with candidemia, some authors 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 CVC. This is discussed in detail separately. (See ["Management of candidemia and invasive candidiasis in adults"](#).)

COLONY STIMULATING FACTORS

Colony stimulating factors (CSFs; also known as myeloid growth factors or hematopoietic growth factors), such as granulocyte and granulocyte-macrophage colony stimulating factors (G-CSF and GM-CSF), are **not** recommended for routine use in patients with established fever and neutropenia. The Infectious Diseases Society of America (IDSA) guidelines recommend against their use for all patients with established fever and neutropenia [1], whereas the American Society of Clinical Oncology and National Comprehensive Cancer Network guidelines state that their use can be "considered" for patients at high risk for infection-associated complications or who have prognostic factors that are predictive of a poor clinical outcome [55,94]. As the available data do not show a clear benefit, we agree with the IDSA guidelines and do not use CSFs in patients with established fever and neutropenia. These issues are discussed in greater detail separately. (See ["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"](#), section on 'Neutropenic fever'.)

MYELOID RECONSTITUTION SYNDROME

Clinicians should be aware of the myeloid reconstitution syndrome, a circumstance in which there may be onset or progression of an inflammatory focus defined clinically or radiologically that manifests at the time of neutrophil recovery [95]. Because such processes may appear in the context of a persistent neutropenic fever syndrome, the likelihood of superinfection must be considered with respect to the antimicrobial spectrum of the patient's current empiric antibacterial therapy and the microbiologic differential diagnosis applicable to those circumstances. (See ["Overview of neutropenic fever syndromes"](#), section on 'Neutropenic fever syndromes'.)

OUTCOMES

The efficacy of the treatment of patients with neutropenic fever syndromes has improved greatly as demonstrated by a progressive decline in mortality rates since the prompt initiation of empiric coverage was implemented in the 1970s [15,96,97]. Studies from the 1960s, before the routine use of empiric therapy, documented mortality rates of 90 percent in neutropenic patients with bacteremia caused by gram-negative bacilli [98,99]. Sepsis due to *P. aeruginosa* or *E. coli* resulted in death within 48 hours after the first blood culture had been drawn in approximately one-half of patients [100,101].

In contrast, in a study of 41,779 adults with cancer who were hospitalized with neutropenic fever in the United States between 1995 and 2000, the in-hospital mortality was 9.5 percent [102]. The mortality rate depended upon the underlying malignancy: 8 percent in patients with solid tumors, 8.9 percent in patients with lymphoma, and 14.3 percent in patients with leukemia. The number of major comorbid conditions also significantly affected the mortality rate. Patients without any comorbidities had a 2.6 percent risk of dying compared with 10.3 percent for patients with one comorbidity, 21.4 percent for patients with two comorbidities, 38.6 percent for patients with three comorbidities, and 50.6 percent for patients with four comorbidities.

Outcomes are poor in neutropenic patients who are critically ill. In a cohort study conducted in 428 neutropenic patients with severe sepsis or septic shock in France between 1998 and 2008, the hospital mortality was 50 percent [92].

Factors that influence the risk of treatment failure are discussed separately. (See "[Risk assessment of adults with chemotherapy-induced neutropenia](#)", section on 'Risk of treatment failure'.)

PROPHYLAXIS

The prophylaxis of infection in patients at risk for neutropenic fever is discussed elsewhere. (See "[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 "[Prevention of infections in 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](#)".)

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"](#) and ["Society guideline links: Invasive fungal infections"](#).)

INFORMATION FOR PATIENTS

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

Here are the patient education articles that are relevant to this topic. We encourage you to print or 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 topic (see ["Patient education: Neutropenia and fever in people being treated for cancer \(The Basics\)"](#))

SUMMARY AND RECOMMENDATIONS

Background – 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 or fungi that translocate across intestinal mucosal surfaces. Because neutropenic patients are unable to mount robust inflammatory responses, serious infection can occur with minimal symptoms and signs. In such patients, fever is often the 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.)

- **Risk assessment** – It is crucial to assess the risk of serious complications in patients with neutropenic fever, since this assessment will dictate the approach to therapy, including the

need for inpatient admission, intravenous (IV) antibiotics, and prolonged hospitalization. High-risk neutropenic patients are those with an absolute neutrophil count (ANC) <500 cells/microL expected to last >7 days or evidence of ongoing comorbid conditions ([table 1](#)). Profound prolonged neutropenia is most likely to occur in the pre-engraftment phase of hematopoietic cell transplantation (HCT; particularly allogeneic) and in patients undergoing induction chemotherapy for acute leukemia. (See '[Risk of serious complications](#)' above.)

- **Fever is an emergency** – Fever in high-risk neutropenic patients should be considered a medical emergency. Empiric broad-spectrum antibacterial therapy should be initiated immediately after blood cultures have been obtained and before any other investigations have been completed ([algorithm 1](#)). Antibiotics should be administered within **60 minutes** of presentation in patients presenting with neutropenic fever. 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 '[General principles](#)' above and '[Timing of antibiotics](#)' above.)
- **Initial antibiotic selection** – 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 and susceptibility patterns. Ideally, antibiotics should be bactericidal. (See '[General principles](#)' above.)
- **High-risk patients** – For high-risk patients with neutropenic fever, we recommend empiric monotherapy with an antipseudomonal beta-lactam agent, such as [cefepime](#), [meropenem](#), [imipenem](#), or [piperacillin-tazobactam](#) ([algorithm 1](#)) (**Grade 1B**). Because of high rates of resistance, [ceftazidime](#) is no longer used at most centers. (See '[Our approach](#)' above.)
- **Selective use of [vancomycin](#)** – We recommend against the use of vancomycin (or another agent that targets gram-positive cocci) as a standard part of the initial regimen (**Grade 1A**). In contrast, gram-positive coverage should be added in patients with suspected central venous catheter-related infection, skin or soft tissue infection, pneumonia, or hemodynamic instability. For patients with complicated presentations (eg, hypotension; central venous catheter, skin, or soft tissue infections; pneumonia), coverage should be broadened to cover the likely pathogens (eg, resistant gram-negative, gram-positive, and anaerobic bacteria as well as fungi). (See '[Our approach](#)' above and '[Addition of gram-positive coverage](#)' above and '[Antibiotic resistance](#)' above.)

- **Modifying the initial regimen** – Persistent fever alone in an otherwise stable patient is **not** sufficient justification for modification of the initial antibiotic regimen. However, modifications to the initial regimen should be considered for patients at risk for infection with antibiotic-resistant organisms, for patients who are clinically unstable, and for patients who have positive blood cultures that are suggestive of a resistant infection. (See ['Modifications to the regimen'](#) above and ['Persistent fever'](#) above.)
- **Managing persistent fever** – Patients who remain febrile after the initiation of empiric antibiotics should be re-evaluated for possible infectious sources. Management algorithms have been developed for the reassessment of neutropenic patients with persistent fever ([algorithm 2](#) and [algorithm 3](#)). (See ['Modifications to the regimen'](#) above.)
- **Adding an empiric antifungal agent** – We recommend the empiric addition of an antifungal agent for neutropenic patients who are persistently febrile after four to seven days despite broad-spectrum antibacterials and who have no documented source of infection ([algorithm 3](#)) (**Grade 1C**). (See ['Indications'](#) above.)
- **Selecting an empiric antifungal agent** – The choice of antifungal agent for empiric therapy depends upon which fungi are most likely to be causing infection as well as toxicity profiles and cost:
 - For persistently febrile patients who have not been receiving antifungal prophylaxis and who have no obvious site of infection, such as pulmonary nodules, we favor [caspofungin](#) (or another echinocandin) since *Candida* spp is the most likely cause in such patients.
 - For persistently febrile patients with pulmonary nodules or nodular pulmonary infiltrates, invasive mold infection should be strongly suspected. In such patients, we favor a mold-active azole or a lipid formulation of amphotericin B.
 - For persistently febrile patients who have been receiving antimold prophylaxis, a different class of antifungal agent with activity against molds should be used for empiric therapy. (See ['Choice of drug'](#) above.)
- **Catheter removal** – In addition to antimicrobial therapy, we recommend central venous catheter removal for patients with catheter-related bloodstream infections caused by *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida* spp, or rapidly growing nontuberculous mycobacteria (**Grade 1B**). We also recommend central venous catheter removal for patients with catheter-related bloodstream infections with fungi other than *Candida* spp (**Grade 1C**). The central venous catheter should also be removed in patients

with complicated infections (eg, tunnel infection, port pocket infection). (See '[Catheter removal](#)' above and "[Management of candidemia and invasive candidiasis in adults](#)".)

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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: <ul style="list-style-type: none">▪ 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).
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Graphic 67027 Version 15.0

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 dos 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
Microbiologic testing from suspected site(s) of infection	Detection of infectious etiology	Bacterial and fungal stains may be helpful; testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is indicated for all patients during the pandemic
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
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* Digital rectal examination is avoided in neutropenic patients.

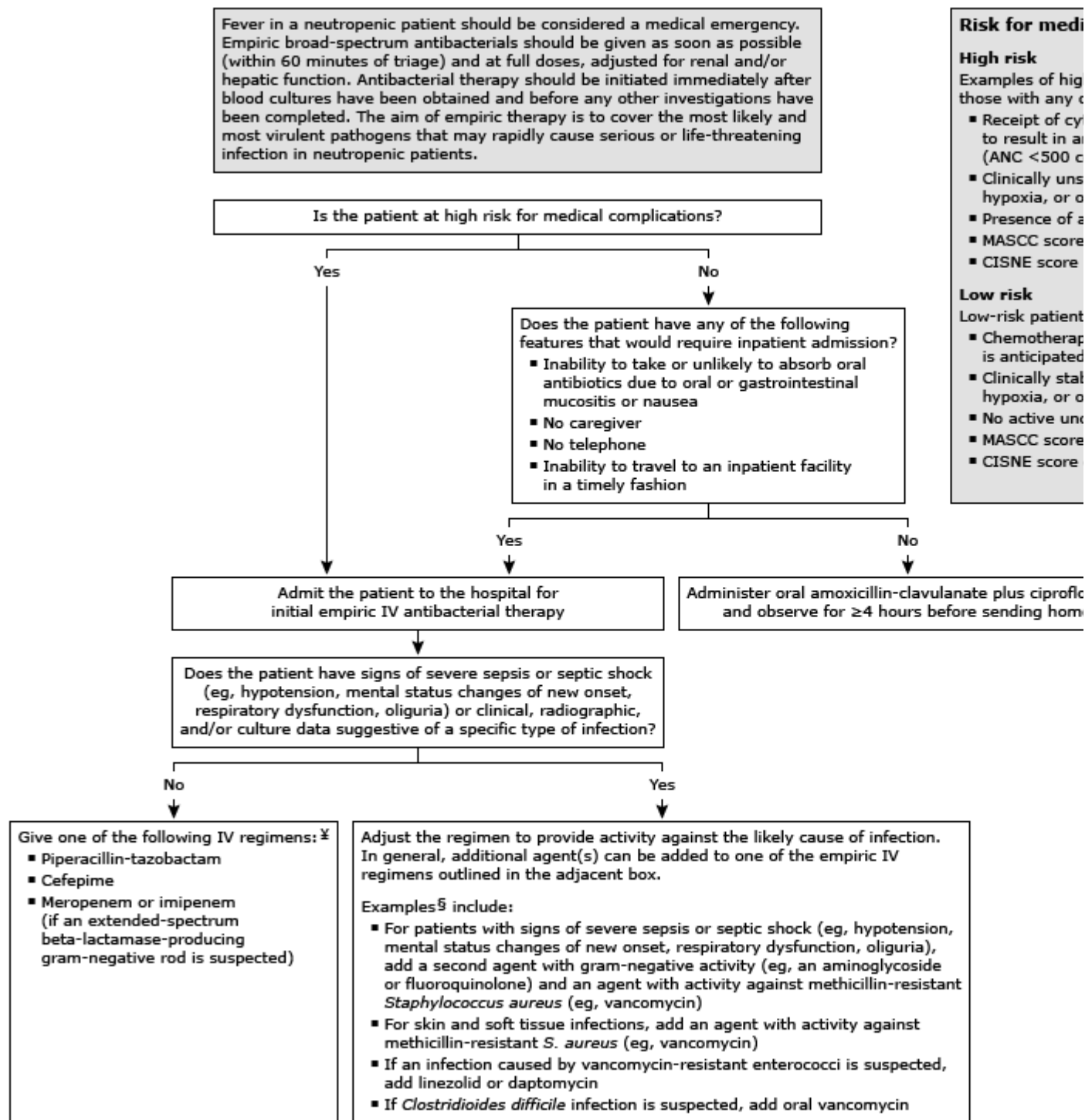
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Range of pathogens encountered in febrile neutropenic patients

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

Initial management of adults with chemotherapy-induced neutropenic fever



ANC: absolute neutrophil count; IV: intravenous; MASCC: Multinational Association for Supportive Care in Cancer risk index; CISNE: Clinical Index of Stable Febrile Neutropenia.

* 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. At the time that the patient presents with neutropenic fever, it is not always possible to anticipate whether the patient will have severe neutropenia for >7 days. Severe prolonged neutropenia is

most likely to occur following induction chemotherapy for acute leukemia and during the pre-engraftment phase of myeloablative hematopoietic cell transplantation (particularly allogeneic).

¶ Examples of active uncontrolled comorbid medical problems include but are not limited to:

- 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

Δ For additional details about the MASCC and CISNE scores, refer to the UpToDate topic review on risk assessment of adults with chemotherapy-induced neutropenia.

◇ Patients with a CISNE score of ≥ 3 are considered to be at high risk for medical complications, those with a score of 1 or 2 are considered to be at intermediate risk, and those with a score of 0 are considered to be at low risk. Intermediate CISNE scores (1 or 2) may require clinicians to judge the relative safety of outpatient oral therapy versus hospitalization for parenteral antibacterial therapy.

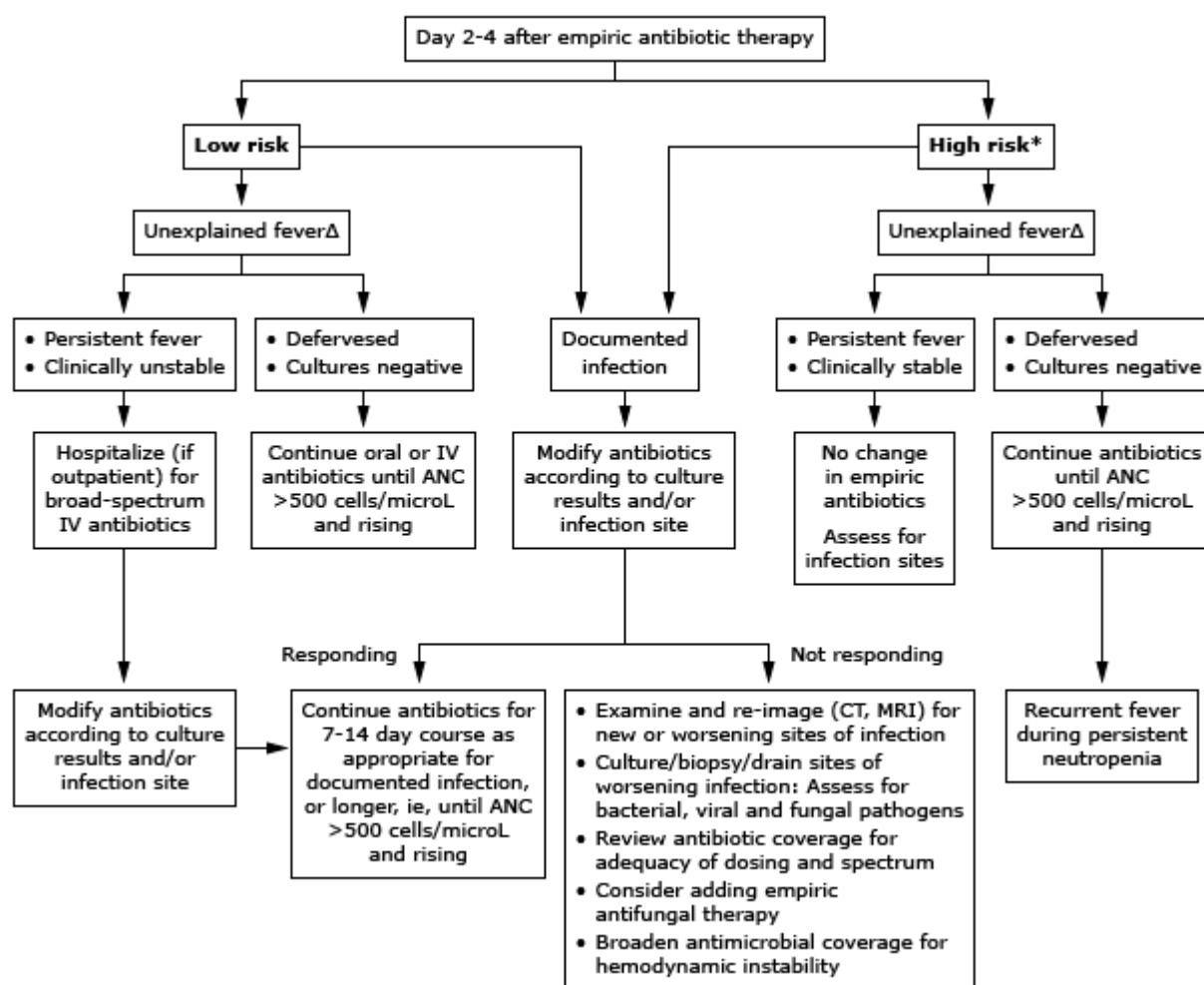
§ The appropriate regimen will depend upon patient-specific factors, including likely site of infection and severity of illness. Some patients will require regimens not included in this algorithm.

¥ Ceftazidime monotherapy has also been shown to be effective and continues to be used at some cancer centers with low rates of resistance. However, UpToDate authors generally avoid ceftazidime monotherapy because of rising resistance rates among gram-negative bacteria and its limited activity against gram-positive bacteria, such as streptococci, compared with newer alternatives. Ceftazidime monotherapy should not be used when there is concern for a gram-positive infection, such as infection caused by viridans group streptococci in patients with severe mucositis.

References:

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. <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.
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Reassessment of the patient with neutropenic fever after two to four days of empiric therapy



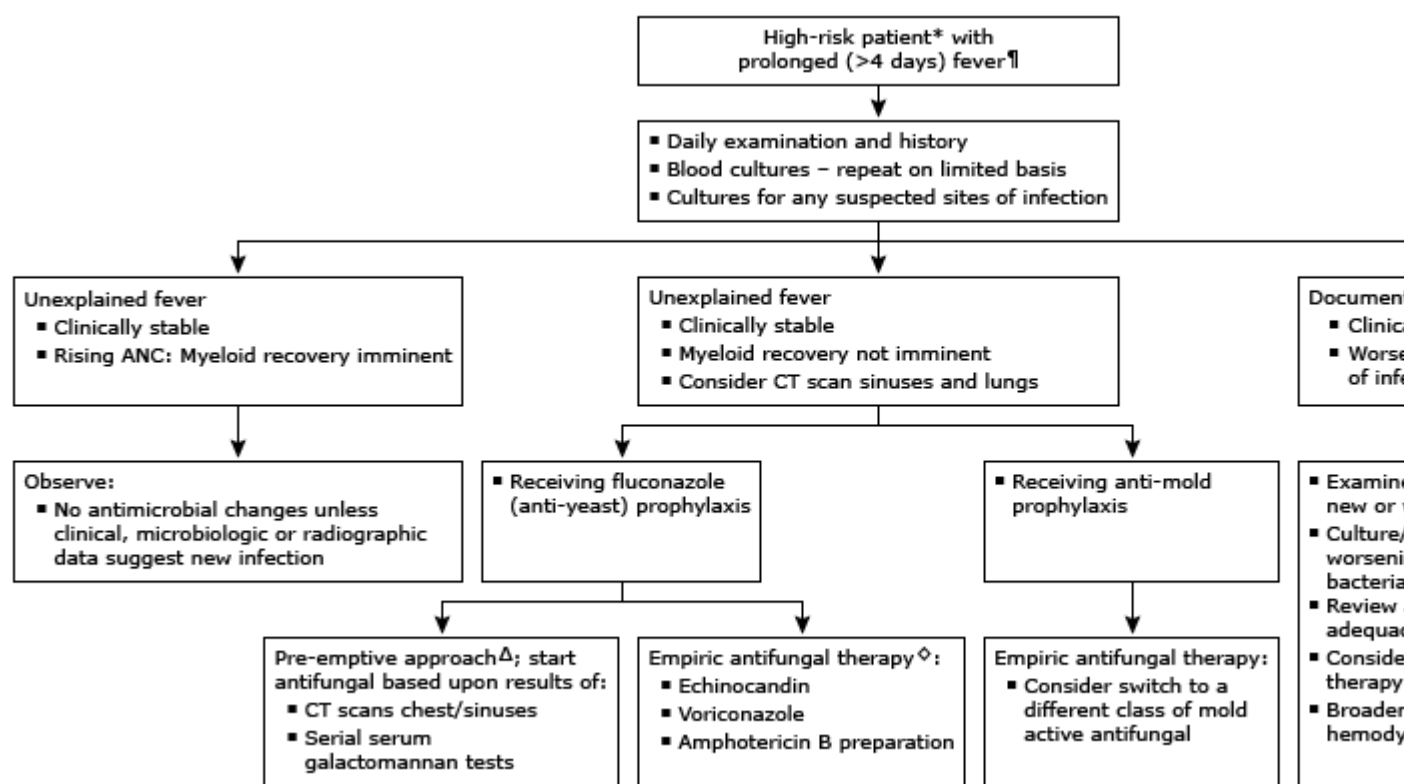
ANC: absolute neutrophil count; CT: computed tomography; IV: intravenous; MRI: magnetic resonance imaging.

* We consider patients to be high-risk if they have either of the following characteristics: neutropenia (ANC <500 cells/microL following cytotoxic chemotherapy) anticipated to last >7 days OR significant comorbid conditions. It should be noted that in the Infectious Diseases Society of America guidelines, an ANC ≤100 cells/microL is used as the cutoff for high-risk neutropenia.

Δ Fever in a neutropenic patient is defined as a single temperature >38.3°C (101°F) or a sustained temperature >38.0°C (100.4°F) for >1 hour.

Adapted with permission from: 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(4):e56-93. Copyright © 2011 Oxford University Press. Available at: www.idsociety.org.

Reassessment of the high-risk patient with persistent neutropenic fever after four days of empiric therapy



ANC: absolute neutrophil count; CT: computed tomography; MRI: magnetic resonance imaging.

* We consider patients to be high-risk if they have either of the following characteristics: neutropenia (ANC <500 cells/microL following cytotoxic chemotherapy) anticipated to last >7 days OR significant comorbid conditions. It should be noted that in the Infectious Diseases Society of America guidelines, an ANC ≤100 cells/microL is used as the cutoff for high-risk neutropenia.

¶ Fever in a neutropenic patient is defined as a single temperature >38.3°C (101°F) or a sustained temperature >38.0°C (100.4°F) for >1 hour.

Δ Limited data to support recommendation.

◇ Spectrum activity and adverse effect profiles vary among antifungals. An echinocandin is often selected for patients without specific concern for infection with mold due to its favorable adverse effect profile. Refer to UpToDate text for detail.

Adapted with permission from: 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(4):e56-93. Copyright © 2011 Oxford University Press. <https://www.idsociety.org/practice-guideline/neutropenic-patients-with-cancer/> (Accessed on March 29, 2023).

