Management of Chemotherapy-Induced Neutropenic Fever

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Abstract: Fever occurs at high rates in patients with chemotherapy-induced neutropenia and is considered an oncologic emergency. Numerous algorithms have been developed to guide treatment decisions. Prompt care and the initiation of empiric antibiotic therapy are critically important universal aspects of these treatment-decision schemata. Fever may be the only sign of infection, as in patients with cancer who are undergoing chemotherapy, the immune response is attenuated. In the majority of cases, no etiology for neutropenic fever is uncovered; nonetheless, a thorough workup is essential. The workup allows practitioners to risk stratify patients as being at low or high risk for infectious complications so that appropriate care can be administered. Although it is important to note that there are management algorithms to follow, every patient may present and respond differently. We generally start with broad-spectrum monotherapy for Gram-negative bacteria and then consider whether Gram-positive or antifungal coverage is necessary based on the clinical picture, including factors such as duration and degree of neutropenia. It is important for all practitioners to understand how to care for patients with neutropenic fever because it is a common and treatable condition.

Keywords: neutropenic fever; malignancy; infection; empiric antibiotics

Introduction

Neutropenic fever is considered an oncologic emergency. Fever in the setting of chemotherapy-induced neutropenia occurs in 10% to 50% of patients with solid tumors and develops in > 80% of those patients who have hematologic malignancies.[1] Prior to the universal implementation of empiric antibiotic therapy, infections accounted for most episodes of neutropenic fever and contributed greatly to mortality. The majority of patients with neutropenic fever do not have documented infections but consensus calls for prompt initiation of empiric broad-spectrum antibiotics because life-threatening infections can be easily masked in this population.[2,3] In this article, we review the definition of neutropenic fever, the pathogenesis and epidemiology of infection, the important aspects of diagnosis, the stratification of patients as being at low or high risk for infectious complications, and discuss treatment management, with particular emphasis on which antimicrobials to use and when to use them. The majority of information we present is drawn from the recommendations of the Infectious Diseases Society of America (IDSA) and the National Comprehensive Cancer Network (NCCN).[4,5] The primary aim of this review is to assist practitioners in making informed decisions regarding the care of oncology patients with neutropenic fever.

Definitions of Neutropenic Fever

Fever in neutropenic patients is defined as a single oral temperature of ≥ 101°F (38.3°C) or a temperature of ≥ 100.4°F (38.0°C) sustained for > 1 hour. Neutropenia is defined

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as an absolute neutrophil count (ANC) < 1000 cells/μL, and profound neutropenia is defined as an ANC < 500 cells/μL or an ANC that is expected to decrease to < 500 cells/μL within 48 hours.[4,5] The longer the duration of neutropenia (ie, > 7 days) and the lower the ANC, the higher the risk of infection. The ANC can be calculated by multiplying the total white blood cell count by the percentage of polymorphonuclear cells and bands.

Pathogenesis

Infections can result from both the direct effects of chemotherapy on mucosal barriers as well as the direct immunosuppressive effects of the underlying malignancy itself.[6] It is important to consider the possibility of autoinfection whenever neutropenic fever occurs. Chemotherapy-induced mucositis occurs from the mouth to the anus. Translocation of gut flora and seeding of the bloodstream is believed to be the most common culprit of neutropenic fever. Impaired humoral immunity occurs in diseases such as multiple myeloma, chronic lymphocytic leukemia, and in patients who have undergone splenectomy, each of which can lead to vulnerability in encapsulated organisms, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*. Depressed cellular immunity is more often associated with lymphomas and lymphocytic leukemia, and can increase the risk of infection by intracellular pathogens, such as *Listeria monocytogenes*, *Salmonella* spp, *Cryptococcus neoformans*, and *Mycobacterium tuberculosis*. Patients receiving prolonged courses (> 4 weeks) of glucocorticoids for lymphomas or leukemia are at risk for *Pneumocystis jirovecii* pneumonia.[6]

Epidemiology

The source for neutropenic fever is often not determined. Fevers typically subside as the neutropenia improves. Clinically documented infections are only found in 20% to 30% of patients.[4] Early on, bacteria is often the culprit, succeeded by antibiotic-resistant bacteria, yeast, and other fungi and viruses.[5]

Bacteria

Bacteremia is the most documented infection seen in patients. It is found in 10% to 25% of patients with neutropenic fever.[4] Common sites of infection include the gastrointestinal (GI) tract, lungs, and skin. Most infections are secondary to Gram-positive organisms, due to the use of long-term central venous catheters. Patients are also at greater risk for Gram-positive bacteremia when given prophylactic antimicrobials directed against Gram-negative pathogens, especially *Pseudomonas aeruginosa*. The most often identified Gram-positive cocci include *Staphylococcus epidermidis* (coagulase-negative being the most common bacterial culture isolates), *Staphylococcus aureus*, viridans group streptococci, and enterococci. Less often seen Gram-positive organisms include *Corynebacterium jeikeium*, *Bacillus* spp, *Leuconostoc* spp, *Lactobacillus* spp, and *Rhodococcus* spp.[7]

Gram-negative bacteremia is associated with a 40% mortality rate among some groups of febrile neutropenic patients.[8] The most frequently identified Gram-negative pathogens include *Escherichia coli*, *Klebsiella* spp, *Enterobacter* spp, *P aeruginosa*, *Citrobacter* spp, *Acinetobacter* spp, and *Stenotrophomonas maltophilia*.[4] Anaerobic infections occur in < 5% of patients with febrile neutropenia.[4]

Fungal Agents

Fungal infections are more common in high-risk patients with neutropenic fever, most often patients with acute leukemia who are receiving induction chemotherapy. Risk factors for fungal infections include prolonged neutropenia, severe neutropenia, prolonged antibiotic use, use of corticosteroids, advanced age, tissue damage, advanced malignancy, and use of indwelling catheters.[7] Fungal infections are associated with persistent (ie, > 7–14 days) or recurrent neutropenic fever. *Candida* spp and *Aspergillus* spp account for most invasive neutropenic fungal infections. *Candida* colonizes the gut and candidemia occurs as a result of translocation across damaged mucosal surfaces secondary to chemotherapy-related mucositis. *Candida* can contribute to catheter-related infections as well, and less often, to esophagitis, hepatitis, hepatosplenic disease, and endocarditis.[4] *Aspergillus* infections result from inhalation of airborne spores into the upper (sinusitis) and lower (pneumonia) respiratory tract, eventually causing hyphal growth. Additionally, mucormycosis can cause severe rhino-orbital-cerebral, pulmonary, and/or disseminated infections in immunocompromised hosts. Endemic fungal infections such as *Blastomyces dermatitidis*, *Histoplasma capsulatum*, and *Coccidioides* spp are subject to reactivation in patients who have been treated with prolonged glucocorticoid use or have immunosuppression. *Trichosporon beigelii*, a yeast pathogen, is increasingly found in in this population, as well. *Fusarium* spp and *Scedosporium* spp are also notable pathogens with high mortality rates.[9,10]

Viral

Reactivation of latent herpes simplex virus type 1 and 2 infections are common in high-risk patients with febrile neutropenia. The viruses present as ulcerations of the

oral or esophageal mucosa, and ulcers/vesicles of the buccal mucosa, genitalia, skin, or perianal areas. Other manifestations include pneumonia, esophagitis, hepatitis, encephalitis, meningitis, and erythema multiforme. Herpes zoster can have an atypical presentation in the immunocompromised population and often spreads across dermatomes. The lungs can also be affected, and respiratory isolation may be recommended. In patients who have received stem cells, Epstein-Barr virus, cytomegalovirus, and human herpesvirus 6 may be reactivated. In addition, respiratory virus infections are more severe and prolonged in this population, including influenza, respiratory syncytial virus, parainfluenza virus, adenovirus, and metapneumovirus.

Diagnosis

History

Fever may be the only symptom of an infection in neutropenic patients because the inflammatory response is often attenuated in this immunocompromised population.[4–7] Taking a careful and targeted patient history is critical. Inquiries about any new signs or symptoms should be made and include organ-specific questions. It is important to note whether the patient has been taking antibiotic prophylaxis. The date and time of the patient's most recent chemotherapy treatment is needed to accurately predict the ANC. It should be noted that if the patient has had previous infections, especially with drug-resistant organisms, and it should be kept in mind that fever may also result from a noninfectious etiology.

Physical Examination

A complete physical examination should be performed on the patient with emphasis on susceptible sites, including the skin, tunneled catheters, bone marrow aspirate, biopsy sites, the periodontium, oropharynx, sinuses, lungs, and genital and perineal areas. In febrile neutropenia, signs of inflammation may be absent. Nonetheless, erythema, rash, vesicles, ulcers, mucositis, and perianal fissures may be present. The traditional teaching is to avoid a digital rectal examination as it may introduce infection by damaging the already-fragile mucosa. Thorough examinations should be performed on the patient daily. Initial assessment of a patient with neutropenic fever is detailed in Figure 1.

Laboratory Testing

Evaluation should include a complete blood cell count with white blood cell differential, liver function tests, and a basic metabolic panel, including assessment of blood urea nitrogen and creatinine testing. These tests are necessary for differentiating between low- and high-risk patients with neutropenic fever.[4,11] Additionally, 2 sets of peripheral blood cultures should be drawn, each from a different site, and simultaneously, 1 from each lumen of a tunneled catheter if present. Blood cultures are typically repeated daily in the first 48 hours if the patient remains febrile.[4] Subsequent blood cultures do not need to be drawn daily for persistent fever, but any new fever after initial defervescence should prompt a new set of blood cultures. Urinalysis and reflex urine culture should be included in the fever workup if signs or symptoms of a urinary tract infection exist or a catheter is in place. If clinically indicated, specimens should be obtained from sputum, cerebrospinal fluid, skin, and stool. In the setting of diarrhea, the presence of *Clostridium difficile* should be investigated. Skin lesions can be biopsied for bacterial, fungal, and viral stains and cultures. If a productive cough is present, sputum can be sent for bacterial and fungal cultures and for a respiratory viral panel (adenovirus, influenza A, influenza B, respiratory syncytial virus, parainfluenza, rhinovirus, metapneumovirus, and *Bordetella pertussis*, when available). In the setting of unresolving lung infiltrates, a bronchoscopy with lavage and possibly percutaneous biopsy or, potentially, thorascopic lung biopsy (if the patient has an adequate platelet count) may be indicated.[5] If meningitis is suspected, a timely lumbar puncture should be performed and cerebrospinal fluid should be processed for appropriate testing. The timing of these tests in the course of a neutropenic fever is discussed in a separate section of this article.

Imaging Tests

The IDSA recommends obtaining a chest radiograph for patients with respiratory signs and symptoms, irrespective of risk status.[4] A chest radiograph is a good place to start evaluation in low-risk neutropenic patients and a chest computed tomography (CT) scan is appropriate for high-risk neutropenic patients with pulmonary symptoms. Such scans are effective in early identification of invasive mold infections in patients with prolonged neutropenia.[12,13] The IDSA recommends repeat chest imaging for increasing or persistent pulmonary signs and symptoms, including cough, dyspnea, and hypoxia.[4] A CT scan of the sinuses, head, abdomen, and pelvis may be performed if clinically warranted. An abdominal CT scan is especially useful for detecting typhlitis (neutropenic enterocolitis) in a patient with abdominal symptoms and persistent fever.

Identifying Risk

Risk assessment during the initial patient evaluation determines the approach to therapy, including the requirement for

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inpatient admission and intravenous (IV) antibiotics. The next sections describe 3 different models of risk assessment: the Multinational Association of Supportive Care in Cancer (MASCC) Risk Index, the IDSA model, and the NCCN model. Table 1 compares the 3 risk models.

The MASCC Risk Index

The MASCC Risk Index (Table 2) is a validated tool for measuring the risk of neutropenic fever–related medical complications.[9,14,15] The index, based on a multinational study of > 1100 patients with neutropenic fever, identifies characteristics that predict risk for severe medical complications. Points are listed next to each category in Table 2. A score ≥ 21 predicts patients with a low risk of complications and for whom outpatient management may be appropriate. A score < 21 predicts patients at high risk for complications. A prospective study validated the MASCC Risk Index by demonstrating that it correctly classified low- and high-risk patients in 98% and 86% of cases, respectively, giving the index a sensitivity of 95%, specificity of 95%, and positive and negative predictive values of 98% and 86%, respectively.[15]

It is important to note that the MASCC Risk Index takes the patient's age and history of fungal infections into consideration, whereas the NCCN and IDSA models do not. However, the MASCC Risk Index does not include duration of neutropenia. In addition, the definition of "burden of illness" may be open to interpretation, making standardization more difficult.

IDSA Risk Assessment

According to the IDSA model, low-risk patients are defined as those who are expected to be neutropenic for ≤ 7 days in the absence of comorbidities or significant hepatic or renal dysfunction. Low-risk patients usually have a MASCC Risk Index score ≥ 21.

High-risk patients are defined as patients with an ANC ≤ 100 cells/μL for > 7 days; evidence of renal dysfunction (creatinine clearance < 30 mL/min) or hepatic

Table 1. Similarities and Differences Between Risk-Assessment Models

Variable	Risk-Assessment Models		
	MASCC Risk Index	**IDSA Model**	**NCCN Model**
Clinical instability	Hypotension and dehydration are negative prognostic indicators	High risk: evidence of sepsis	High risk: clinically unstable
Comorbidities	No chronic obstructive pulmonary disease better	Low risk: absence High risk: clearly defined organ system–based comorbidities, including lung disease	Low risk: no comorbidities requiring hospitalization
Hepatic or renal dysfunction		High risk: if present	High risk: if present
Type of tumor	Solid tumor better	Low risk: solid tumor High risk: AML or alloSCT	
History of infection	No history of fungal infections better		
Presence of current infection		High risk: presence of intravascular catheter infections, pulmonary infections	High risk: current pneumonia or complex infection
Age	Age < 60 years better		
Outpatient or inpatient status	Outpatient better		Low risk: outpatient High risk: inpatient
Degree and duration of neutropenia		Low risk: neutropenia for ≤ 7 days High risk: ANC ≤ 100 cells/μL for > 7 days	Low risk: ANC ≤ 100 cells/μL for < 7 days High risk: ANC ≤ 100 cells/μL for ≥ 7 days
ECOG performance status			Low risk: 0–1
MASCC Risk Index score	Low risk: ≥ 21 High risk: < 21	Low risk: ≥ 21 High risk: < 21	Low risk: ≥ 21 High risk: < 21
Alemtuzumab			High risk: if administered in past 2 months
Grade 3 or 4 mucositis			High risk: if present

Abbreviations: alloSCT, allogeneic stem cell transplantation; AML, acute myeloid leukemia; ANC, absolute neutrophil count; ECOG, Eastern Cooperative Oncology Group; IDSA, Infectious Diseases Society of America; MASCC, Multinational Association of Supportive Care in Cancer; NCCN, National Comprehensive Cancer Network.

Table 2. The Multinational Association of Supportive Care in Cancer Risk Index

- Burden of illness (the general clinical status of the patient at presentation)
  - No or mild symptoms: 5
  - Moderate symptoms: 3
  - Severe symptoms or moribund: 0
- No hypotension (systolic blood pressure < 90 mm Hg): 5
- No chronic obstructive pulmonary disease: 4
- Solid tumor or hematologic malignancy with no history of fungal infections: 4
- No dehydration or requirement of parenteral fluids: 3
- Outpatient status at the time of onset of the neutropenic fever syndrome: 3
- Age < 60 years: 2

dysfunction (aminotransferase levels > 5 times the upper limit of normal). Other high-risk comorbid conditions include: GI mucositis, hemodynamic instability, uncontrolled GI symptoms (eg, abdominal pain, nausea, vomiting, or diarrhea), underlying lung disease, neurologic or mental status changes, IV catheter infection, new pulmonary infiltrates, or hypoxia. Patients receiving induction chemotherapy for acute myeloid leukemia or conditioning for allogeneic stem cell transplantation are also at high risk for life-threatening infections secondary to expected prolonged neutropenia.

Afebrile neutropenic patients who have new signs or symptoms suggestive of infection should be treated as high-risk patients.[4] High-risk patients warrant admission to the hospital for treatment with IV antibiotics. Patients with evidence of sepsis should be regarded as high risk and managed with IV antibiotics. Low-risk patients, on the other hand, can potentially be managed with an outpatient course of antibiotics.[4,16]

NCCN Risk Assessment

The NCCN model defines a patient as low risk if most of the following criteria are met: outpatient status at time of start of fever; no comorbidities requiring hospitalization; anticipated short duration of severe neutropenia (ANC ≤ 100 cells/μL expected to last < 7 days); Eastern Cooperative Oncology Group performance status 0 or 1; neither renal nor hepatic insufficiency; or a MASCC Risk Index score ≥ 21.[5] Per the NCCN model, a patient is considered to be high risk if any of the following criteria are met: inpatient status at time of start of fever; significant medical comorbidities or instability; expected prolonged neutropenia (ANC ≤ 100 cells/μL lasting ≥ 7 days); hepatic insufficiency (aminotransferase levels > 5 times the upper limit of normal) or renal insufficiency (creatinine clearance < 30 mL/min); uncontrolled progressive cancer, pneumonia, or other complex infection; alemtuzumab administration within the past 2 months; grade 3 or 4 mucositis; or a MASCC Risk Index score ≤ 21.

Management

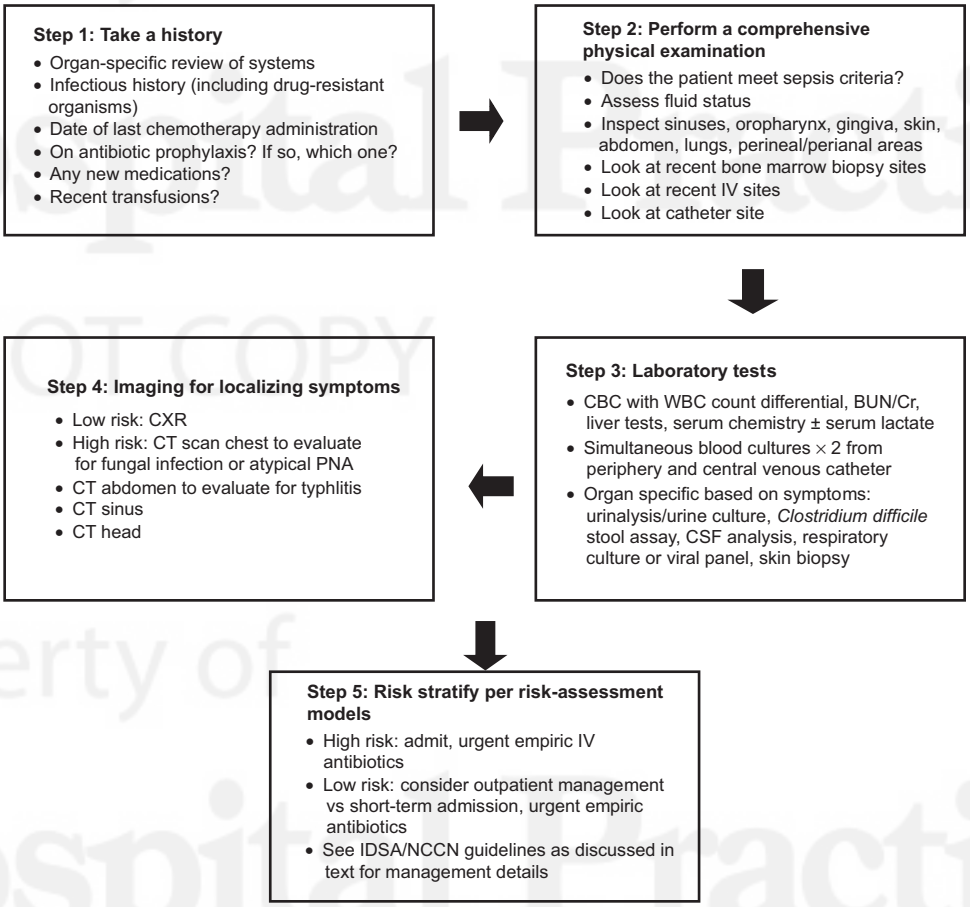
Oncologists should instruct patients to take any fever seriously, especially in the setting of recent chemotherapy. If the patient comes to the hospital, triage and emergency department providers should ask about the temporal relationship between chemotherapy administration and onset of fever, as it may predict neutropenia.[17] The ANC usually reaches a nadir at a median of 7 to 10 days from the initiation of chemotherapy; it may be shorter or longer depending on the type of malignancy, the chemotherapy, the cycle number, and the status of the bone marrow prior to initiation of chemotherapy.[18] The next step is to quickly recognize systemic inflammatory response syndrome or sepsis. These diagnostic tests and the patient's clinical picture will identify the patient's risk for serious medical complications and guide antimicrobial therapy.

No single empiric initial regimen for febrile neutropenia has been developed despite decades of clinical trials.[4,19] Broad-spectrum antibacterial agents should be given as soon as possible and at full doses, adjusted for renal and hepatic function, to cover the most likely and deadly pathogens. Antibiotics should cover known or suspected infections. Initial selection of antibiotics should be guided by the patient's history, symptoms, signs, drug allergies, recent antibiotic use (including prophylaxis), previous infections (especially if antibiotic-resistant pathogens were present), and the institution's susceptibility pattern of common pathogens. Therapy should be adjusted based on clinical response and culture results. Chemotherapy may need to be temporarily withheld during this time. Neutropenic patients with worsening clinical picture in the absence of fever should be treated with IV antibiotics as well.[4] Antibiotics should be administered promptly within 1 to 2 hours of presentation.[4,20,21]

Initial Treatment Regimen

The initial treatment regimen for neutropenia includes monotherapy with an antipseudomonal β-lactam agent, such as cefepime, meropenem, imipenem/cilastatin, or piperacillin/tazobactam. Ceftazidime monotherapy is generally avoided as it may confer higher resistance to Gram-negative bacteria later on in a patient's course of treatment. Ceftazidime also has decreased potency against Gram-negative organisms and limited efficacy against Gram-positive bacteria, such as

Figure 1. Initial assessment of a patient with neutropenic fever.



Abbreviations: BUN, blood urea nitrogen; CBC, complete blood cell count; Cr, serum creatinine; CSF, cerebrospinal fluid; CT, computed tomography; CXR, chest radiograph; IDSA, Infectious Diseases Society of America; IV, intravenous; NCCN, National Comprehensive Cancer Network; PNA, pneumonia; WBC, white blood cell.

streptococci.[4] Aminoglycoside monotherapy is contraindicated because of the emergence of microbial resistance to this class of antimicrobial agents.[4]

Per the NCCN model, a second approach to initial empirical therapy is combination IV antibiotic therapy using 3 options: 1) aminoglycoside plus an extended-spectrum antipseudomonal penicillin; 2) ciprofloxacin plus an antipseudomonal penicillin; or 3) aminoglycoside plus an extended-spectrum antipseudomonal cephalosporin (ceftazidime or cefepime).[5]

However, there is strong evidence to support use of monotherapy with a β-lactam that acts against *Pseudomonas* spp compared with using a 2-drug regimen.[22,23] This strategy is due in part to the improved intrinsic efficacies of antibiotics, such as piperacillin/tazobactam, cefepime, or the carbapenems, compared with agents used 20 years ago.[24] In addition, newer, more effective chemotherapy regimens and the use of myeloid stimulating factors have contributed to improved outcomes.[24] Specifically, monotherapy with a β-lactam was compared with β-lactam–aminoglycoside combination therapy, and monotherapy resulted in fewer adverse events.[25] In comparison with each other, cefepime is equivalent to imipenem.[26] Bow et al[27] found pipercillin/tazobactam therapy to be superior to treatment with cefepime. Despite prior controversy regarding cefepime use increasing 30-day mortality, an analysis completed by the US Food and Drug Administration (FDA) did not confirm the negative assessment of cefepime, and thus, the IDSA recommends cefepime as initial monotherapy.[4,28] In our practice, we generally start with cefepime or piperacillin/tazobactam and modify accordingly.

Pneumonia in neutropenic patients should be treated as a health care–acquired infection according to the American Thoracic Society.[29] Initial broad-spectrum treatment with combinations of an antipseudomonal β-lactam or carbapenem, plus an aminoglycoside or antipseudomonal

fluoroquinolone, is the recommended treatment for neutropenic patients with pneumonia. Vancomycin is added for empiric therapy if methicillin-resistant *S aureus* (MRSA) is suspected. Treatment with linezolid should be considered for patients who do not improve with vancomycin therapy and who are known to be colonized with vancomycin-resistant enterococci (VRE) or have MRSA or VRE isolated from respiratory specimens.[5,30–32]

If the patient is initially clinically unstable, the NCCN guidelines recommend a broad-spectrum β-lactam plus an aminoglycoside and vancomycin. If the patient is not on antifungal prophylaxis, the addition of fluconazole or an echinocandin should be considered.

For patients allergic to penicillin, unless a patient has a history of hives and/or bronchospasm, cephalosporins are usually well tolerated.[4] Newer studies have found that cephalosporins and carbapenems may be safer to administer in penicillin-allergic patients than previously expected.[33,34] However, in those instances of severe allergy, combinations of ciprofloxacin and clindamycin or aztreonam and vancomycin can be used.[4]

When to Add Gram-Positive Coverage

Addition of Gram-positive coverage to the initial empiric antibiotic regimen has not shown significant clinical benefit, likely because the most common pathogen is coagulase-negative staphylococci and it rarely causes rapid deterioration[4,35,36]; however, MRSA presents a real concern. Vancomycin is the usual drug of choice for Gram-positive coverage. The uncontrolled use of vancomycin has led to the development of resistant organisms. There are specific indications for the therapeutic addition of Gram-positive coverage. The IDSA recommends the use of vancomycin or Gram-positive coverage in the following circumstances: 1) hemodynamic instability or other signs of sepsis; 2) pneumonia; 3) positive blood cultures; 4) suspected central venous catheter infections; 5) skin or soft tissue infections; and 6) the use of fluoroquinolone prophylaxis in patients with mucositis taking ceftazidime as monotherapy. Patients with a history of MRSA, VRE, or other resistant streptococci infections should also receive appropriate Gram-positive coverage.[4] Additionally, the NCCN recommends Gram-positive coverage in those patients with known colonization with penicillin- or cephalosporin-resistant pneumococci or MRSA. The NCCN notes that the combination of severe mucositis in patients who previously received prophylaxis with quinolones or trimethoprim/sulfamethoxazole causes an increased risk for viridans group streptococcal bacteremia.[5] Other agents with broad-spectrum activity against Gram-positive pathogens include linezolid, daptomycin, and quinupristin/dalfopristin. These antibiotics cover β-lactam– and vancomycin-resistant pathogens. The use of these drugs should be confined to infections with positive cultures for vancomycin-resistant organisms or for patients for whom vancomycin may not be an option.[5] Linezolid has a higher risk of causing myelosuppression, especially when given for > 14 days.[5] Daptomycin is another option but is less efficacious with regard to pulmonary infections because it is inactivated by surfactants.[5] Rarely, it can also cause increases in creatinine kinase.[5] Daptomycin can be used for the treatment of complicated skin infections.[5] Other agents to consider are quinupristin/dalfopristin; tigecycline and telavancin are not well studied in patients with cancer[5] and do not have a proven role in routine empirical coverage.[4]

Outpatient Management

Neither the IDSA nor the NCCN endorses initial outpatient management of neutropenic fevers but rather proposes at least a short stay (2–12 or 12–24 h) at an ambulatory facility or hospital for observation and management. Patients who are clinically stable and deemed to be at low risk for sustaining complications (based on previously described risk-assessment models) can be discharged home with close follow-up. If outpatient management is chosen, close observation and prompt access to a health care provider are necessary. The IDSA and NCCN recommend ciprofloxacin plus amoxicillin/clavulanate as an appropriate outpatient regimen for low-risk patients.[4,5,37] Ciprofloxacin monotherapy provides suboptimal coverage for Gram-positive organisms and carries the potential risk of breakthrough viridans group streptococci infections as previously discussed.[4,5,38] For penicillin-allergic patients, ciprofloxacin plus clindamycin is acceptable.[5,39] The outpatient management of febrile neutropenia is still under debate. Admission or readmission is required immediately for persistent fever or signs and symptoms of worsening infection.[4]

Modifications to the Treatment Regimen

Changes to the initial regimen should be based on the following criteria:

- Evolving clinical and microbial data (including susceptibility);
- Patients with blood cultures that are negative for 2 to 3 days may discontinue vancomycin;

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- If the patient becomes hemodynamically unstable, consider broadening therapeutic coverage to include resistant Gram-positive and Gram-negative coverage, anaerobes, and fungi;
- Persistent fever > 4 days with no identified source indicates that empiric antifungal coverage may be necessary;
- Stable, low-risk patients on IV or oral antibiotics in the hospital may simplify their regimen and potentially transition to the outpatient setting;
- Clinically stable patients with good GI absorption can be switched from IV to oral antibiotics;
- Chemotherapy-induced oral ulcerations or esophagitis may be worsened by herpes simplex virus or *Candida* spp infections, so empiric acyclovir and/or fluconazole may be appropriate;
- Neutropenic enterocolitis is characterized by fever, diarrhea, and abdominal pain, and is called typhlitis when the cecum is involved. It is caused by chemotherapy-induced damage to the intestinal mucosa in the setting of neutropenia and can rapidly progress to sepsis.[40] Patients should be treated with an expanded broad-spectrum antimicrobial regimen that covers anaerobes, especially *C difficile*, with metronidazole. The NCCN guidelines recommend initial oral metronidazole for *C difficile* colitis that is not severe.[5,41]

Unexplained persistent fever in a stable patient rarely necessitates a change in the initial regimen.

Persistent Fever

The median time to defervescence following the initiation of empiric antibiotic therapy is 2 days in oncology patients with solid tumors and 5 days in patients with hematologic malignancies or stem cell transplantations.[4,27,42] It is important to keep in mind both infectious and noninfectious causes of persistent fever. The noninfectious etiologies include thrombosis, large hematoma, drug fever, transfusion fever, or uncontrolled malignancy. Lack of initial response to therapy can be due to inadequate tissue or serum levels of the antimicrobial agent, > 1 infection, or viral or fungal infections, among other reasons. The IDSA has developed algorithms for the treatment of persistent fever lasting > 2 days and > 4 days,[4] which take into account the risks to the patient, whether there is a documented infection, if the patient is hemodynamically stable, and the proposed duration of neutropenia. Further recommendations from the NCCN have been added.[5]

Low- or High-Risk Patients With Persistent Fever Following > 2 to 4 Days of Empiric Antibiotic Therapy

If the low-risk patient is clinically unstable, hospitalization is recommended for administration of IV antibiotics (standard regimen).[4] As needed, the antibiotic regimen can be modified. If the high-risk patient is clinically stable, the current antibiotic regimen should be maintained and assessment for sites of infection should be continued. If the patient defervesces and laboratory cultures are negative, the patient can be continued on oral or IV antibiotic therapy until an ANC > 500 cells/μL is achieved.[4] If the patient has a documented infection, the antibiotic regimen should be modified as needed per culture results. If the patient is responding well, antibiotics should be continued for a ≥ 7- to 14-day course until an ANC > 500 cells/μL is reached.[4] The NCCN guidelines further clarify the duration of antimicrobial therapy for documented infections. In some instances, the duration of therapy may last longer than the duration of neutropenia, depending on the site of infection and the pathogen. For example, lung or sinus infections, typhlitis, or invasive mold infections may require longer courses of treatment.[5] If the patient's infection is not responding, re-imaging with CT scan/magnetic resonance imaging for new or worsening evidence of infection should be performed.[4] The patient should also be re-cultured for bacterial, viral, and fungal pathogens. The clinician should review available antibiotic therapy for spectrum of coverage and appropriate dosing. Consideration should be given to adding on antifungal therapy.[4,5] Broader antimicrobial coverage for any hemodynamic instability is indicated along with consultation with an infectious disease specialist.[5]

High-Risk Patients With Persistent Fever > 4 Days Following Initiation of Empiric Antibiotic Therapy

Daily examination of the patient should be performed and blood cultures should be repeated on a limited basis, especially culturing for any suspected sites of infection.[4] If the patient is clinically stable and has an increased ANC, then continued observation with no changes to the regimen should be followed unless clinical, microbiologic, or radiologic data suggest a new infection.[4] If the patient is clinically stable and myeloid recovery does not seem imminent, CT scans of the sinuses and lungs should be considered to evaluate for invasive mold infections.[4] If the patient has a documented infection and is hemodynamically unstable with worsening signs of infection, then re-imaging, re-culturing, and a broader spectrum of antibiotic therapy (please see the section on antifungal treatment) along with consultation with an infectious disease specialist are indicated.[5]

Antibiotic Resistance

For patients with persistent fever, it is important to continue checking culture sensitivities because acquired resistance and multidrug-resistant organisms are increasingly common.[8,21,43–45] Routine use of prophylactic antibiotics has been linked to an increased risk of resistant pathogens.[46,47] Higher risk of resistance is conferred in those patients with previous infection or colonization with drug-resistant microbes, and in hospital settings where high rates of resistance have been documented. Antibiotic stewardship programs can assist in using appropriate antibiotics and slowing the development of resistance by limiting prophylaxis, using targeted antibiotics, and discontinuing antibiotics at the appropriate time.[48] Increasingly, antibiotic-resistant organisms are emerging as the cause of bloodstream infections in neutropenic patients. In patients at high risk of developing mucositis, such as patients on induction regimens for acute leukemia and those taking prophylactic ciprofloxacin or trimethoprim/sulfamethoxazole, there is a higher risk of viridans group streptococcal infection.[38] The increase in such infections likely has resulted from the limited Gram-positive coverage provided by these antibiotics, thereby allowing for GI colonization followed by infection.[5] Notably, viridans group streptococci is known for causing septic shock and acute respiratory distress syndrome.[38,49] Also, due to the frequent use of fluoroquinolone prophylaxis, quinolone-resistant *E coli* is becoming a more common cause of bacteremia.[50] Fluoroquinolone overuse is linked to colonization by MRSA, thereby increasing the risk of subsequent infection. Vancomycin use increases the risk of colonization by VRE.[44] Extended-spectrum β-lactamase–producing *E coli* has been linked to exposure to cephalosporins, aminoglycosides, or flouroquinolones.[51] Patients with malignancies receiving fluoroquinolone prophylaxis are at high risk of colonization and subsequent bacteremia from these highly resistant organisms.[52]

The IDSA guidelines indicate use of vancomycin, linezolid, or daptomycin for MRSA infections. Linezolid or daptomycin can be used to treat VRE but daptomycin is not FDA-approved for this indication.[5] For extended-spectrum β-lactamase–producing Gram-negative bacilli, imipenem or meropenem can be used. For carbapenemase-producing bacteria, including *Klebsiella pneumoniae* carbapenemase, polymyxin/colistin or tigecycline is indicated for treatment.[4]

Empiric Antifungal Coverage

In patients with persistent neutropenic fever lasting $>$ 4 days with an expected total duration of neutropenia $>$ 7 days, adding empiric antifungal therapy is recommended. Older studies, from 1960 to 1980, revealed that undiagnosed fungal infections were found on autopsy in 66% of patients who died with prolonged neutropenia.[53] Moreover, later studies have shown that the incidence of fungal infections secondary to *Candida or Aspergillus* spp increased following $>$ 7 days of persistent neutropenic fever.[54,55] When the clinical perception is that the patient is unstable or may have a fungal infection, empiric antifungal therapy should be started as soon as suspected.[56]

Choosing which antifungal to use depends on the most likely etiology of infection, toxicity profile, cost, and prior studies demonstrating efficacy of specific antifungal drugs. In patients who have not been receiving antifungal prophylaxis, *Candida* spp is the most likely cause of infection. In patients who have been receiving fluconazole, either fluconazole-resistant *Candida* spp (eg, *Candida glabrata* and *Candida krusei*) or invasive mold infections, such as *Aspergillus* spp, are the most likely culprits; other molds underlying infection include zygomycosis and fusariosis.

The IDSA recommends that empiric fungal therapy include micafungin, caspofungin, voriconazole, itraconazole, or the lipid formulation of amphotericin B (amphotericin B deoxycholate). Amphotericin B was once the standard of care for treating fungal infections; the liposomal form was found to be efficacious and less toxic and became the preferred choice.[57] Caspofungin was compared with liposomal amphotericin B in a randomized, double-blind study and both had overall success rates of 34%; however, lower mortality rates were seen in the caspofungin group (11% vs 44% with liposomal amphotericin B), which demonstrated the efficacy of caspofungin as initial antifungal treatment.[58] Caspofungin does not have effective antifungal activity against *Cryptococcus* spp, *Trichosporon* spp, *Fusarium* spp, *Histoplasma* spp, *Blastomyces* spp, or *Coccidioides* spp. Posaconazole is approved by the FDA for the prophylaxis of fungal infections in neutropenic patients and for treating mucocutaneous candidiasis but it has not been studied for the empiric treatment of invasive fungal infections in patients with neutropenic fever.

The IDSA and NCCN guidelines recommend an echinocandin, such as caspofungin, as initial therapy for candidemia in most neutropenic patients.[4,5,59] If empiric treatment that offers coverage for *Aspergillus* spp is needed, voriconazole is the recommended agent.[5,60,61] Voriconazole serum levels of $\geq$ 1 to 5.5 μg/mL are thought to be required for efficacy and patients should be monitored in cases of refractory disease or drug toxicity.[62] For breakthrough invasive aspergillosis, optimal therapy may include switching to liposomal

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amphotericin B.[5,61] For salvage therapy, liposomal amphotericin B, itraconazole, posaconazole, caspofungin, or micafungin can be considered, but more research is needed in the use of empiric antifungal treatment for aspergillosis.[61] If zygomycosis or mucormycosis is suspected, liposomal amphotericin B is recommended because voriconazole does not provide adequate coverage.[5] Infection with *Fusarium* spp is more likely to occur in the setting of cutaneous disseminated fungal lesions and blood culture isolation of mold.[63] Therapy may include voriconazole,[64] posaconazole,[65] or liposomal amphotericin B.[66] *Scedosporium* spp is resistant to amphotericin B and should be treated with itraconazole, voriconazole, or posaconazole.[67,68]

The practice of empiric antifungal therapy is expensive and can be toxic. The preemptive approach is more targeted: only if there is radiologic evidence or positive serum fungal diagnostic tests, or both, is an antifungal agent initiated in an attempt to prevent invasive fungal infection.[4,5] The 2 serum fungal diagnostic tests are the (1,3)-β-D-glucan assay and the galactomannan assay, but the reliability of these tests is questionable. The (1,3)-β-D-glucan assay detects *Candida* spp, *Aspergillus* spp, *Pneumocystis* spp, and *Fusarium* spp (but not the zygomycetes or *Cryptococcus* spp).[4] In a study from 2008 of patients with acute leukemia,[69] the (1,3)-β-D-glucan assay had a sensitivity of 63% and a specificity of 96% for invasive fungal infections.[69] The galactomannan assay detects only *Aspergillus* spp.[4]

Concomitant use of piperacillin/tazobactam can cause false-positive result rates and anti-mold antifungals can cause high false-negative result rates.[4,70] A meta-analysis showed the sensitivity of the galactomannan test to be 70% and its specificity to be 89%, but the accuracy varied in patients with hematologic malignancies.[71] At our institution, we obtain chest CT scans for persistently febrile patients. The galactomannan test is used when trying to avoid invasive means for investigation of an invasive fungal infection. Both the IDSA and the NCCN do not consider preemptive antifungal therapy the standard of care.[4,24,56] Studies suggest that it does not confer benefit.[72]

Duration of Antibiotic Treatment

If an infectious source is identified, the standard course of antibiotic treatment should be continued (ie, 10- to 14-day course for pneumonia).[4,5] Antibiotics should continue until the ANC is $\geq$ 500 cells/μL.[4] If no source of infection is identified with negative cultures, the duration of antibiotic therapy then depends on the resolution of fever and evidence of neutrophil recovery (ANC $>$ 500–1000 cells μ/L). Alternatively, if the fever resolves but the patient is still neutropenic, the patient can continue the antibiotic regimen to complete an appropriate treatment course. When there is resolution of signs and symptoms of infection, the patient can switch to oral fluoroquinolone prophylaxis until there is marrow recovery.[4]

Catheter Infections

Central venous catheter infections occur frequently in patients with neutropenic fevers. If cultures from the catheter are positive 2 hours before the patient's actual peripheral blood culture shows a positive result—when the samples are drawn simultaneously—then the catheter is likely the source of the infection. Catheter removal is recommended for catheter-related bacteremia from *S aureus*, *P aeruginosa*, fungi, and mycobacteria. A mortality benefit is seen with improved clearance of infection in cases of *S aureus*, *P aeruginosa*, and *Candida* spp.[73–75] The standard of care is antibiotic treatment for 14 days, patient blood sampling to monitor for clearance of blood cultures, and alternating treatment through each lumen of the catheter.[5] Catheter removal is also recommended for tunnel and port pocket infections, septic thrombosis, endocarditis, sepsis with hemodynamic instability, and bloodstream infection that persists despite 72 hours of therapy.[1] Complicated central venous catheter infections warrant treatment with 4 to 6 weeks of antibiotic therapy (ie, deep tissue infection, endocarditis, septic thrombosis, or persistent bacteremia or fungemia occurring $>$ 72 hours following catheter removal in a patient on appropriate treatment).[4] For coagulase-negative staphylococci bacteremia, the catheter does not have to be removed and the patient can be treated with systemic antibiotics with or without antibiotic lock therapy.[4]

Treatment With Myeloid Growth Factors

Neutrophil count recovery is associated with resolution of neutropenic fever. The neutropenia caused by cytotoxic chemotherapy can be prolonged, especially in the pre-engraftment phase of hematopoietic stem cell transplantation and in patients undergoing induction chemotherapy for acute leukemia. The judicious use of granulocyte colony–stimulating factors, such as recombinant human granulocyte colony–stimulating factors, pegylated filgrastim, and granulocyte-macrophage colony–stimulating factors, have been used to reduce the duration of neutropenia. They are generally not recommended for routine use in patients with established fever and neutropenia.[4] Such drugs are given as primary prophylaxis following the administration of chemotherapy when neutropenia is anticipated and specifically

when the anticipated incidence of neutropenic fever is ≥ 20% with a given regimen.[1,4,5,76,77] More specifically, the NCCN recommends (category 2B) considering growth factor support in cases of pneumonia, invasive fungal infections, or any type of progressive infection.[5] In our practice, we administer filgrastim in cases of prolonged or nonresponsive neutropenia in patients who have prolonged infections, especially invasive mold infections. According to the American Society of Clinical Oncology guidelines, the use of colony-stimulating factors should be restricted to patients with high-risk features, such as expected, prolonged (> 10 days), or profound (< 100 cells/μL) neutropenia; age > 65 years; uncontrolled primary disease; pneumonia, hypotension, sepsis, invasive fungal infection; or hospitalization.[76]

Conclusion

Neutropenic fever occurs frequently as a complication of chemotherapy. Fever may be the only symptom that the patient manifests. A detailed history and physical examination coupled with laboratory and diagnostic tests allow for patient risk stratification. These tools help to guide the clinician's choices in antimicrobial therapy use. Prompt initiation of empiric antimicrobial therapy is critical. The algorithms discussed provide evidence-based guidance regarding which antibiotics provide most effective therapy while attempting to prevent drug-resistant microbes. It is recommended that treatment for infection begin with broad-spectrum monotherapy for Gram-negative bacteria that covers the most common culprits, and move on to Gram-positive or antifungal coverage as the clinical picture dictates. The guidelines also allow practitioners to determine when outpatient management is appropriate.

Conflict of Interest Statement

Aarti S. Bhardwaj, MD, and Shyamala C. Navada, MD, disclose no conflicts of interest.

References

1. Klastersky J. Management of fever in neutropenic patients with different risks of complications. *Clin Infect Dis*. 2004;39(suppl 1):S32–S37.
2. Sickles EA, Green WH, Wiernik PH, et al. Clinical presentation in granulopenic patients. *Arch Intern Med*. 1975;135(5):715–719.
3. Schimpff S, Satterlee W, Mae Young V, et al. Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. *N Engl J Med*. 1971;284(19):1061–1065.
4. Freifeld AG, Bow EJ, Sepkowitz KA, et al; Infectious Diseases Society of America. 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–e93.
5. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Prevention and treatment of cancer-related infections. Version 2.2011. http://www.nccn.org. Accessed December 3, 2012.
6. Sepkowitz KA, Brown AE, Telzak EE, Gottlieb S, Armstrong D. Pneumocystis carinii pneumonia among patients without AIDS at a cancer hospital. *JAMA*. 1992;267(6):832–837.
7. Sipsas NV, Bodey GP, Kontoyiannis DP. Perspectives for the management of febrile neutropenic patients with cancer in the 21st century. *Cancer*. 2005;103(6):1103–1113.
8. Klastersky J, Paesmans M, Ameye L, et al. Bacteremia in febrile neutropenic cancer patients. *Int J Antimicrob Agents*. 2007;30(suppl 1): s51–s59.
9. Jahagirdar BN, Morrison VA. Emerging fungal pathogens in patients with hematologic malignancies and marrow/stem-cell transplant recipients. *Semin Resp Infect*. 2002;17(2):113–120.
10. Bow EJ. Invasive fungal infection in haematopoietic stem cell transplant recipients: epidemiology from the transplant physician's viewpoint. *Mycopathologia*. 2009;168(6):283–297.
11. Klastersky J, Paesmans M, Rubenstein, EB, et al. The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol*. 2000;18(16):3038–3051.
12. Heussel CP, Kauczor HU, Heussel GE, et al. Pneumonia in febrile neutropenic patients and in bone marrow and blood stem-cell transplant recipients: use of high resolution computed tomography. *J Clin Oncol*. 1999;17(3):796–805.
13. Caillot D, Casanovas O, Bernard A, et al. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. *J Clin Oncol*. 1997; 15(1):139–147.
14. Paesmans M, Klasterky J, Maertens J, et al. Predicting febrile neutropenic patients at low risk using the MASCC score: does bacteremia matter? *Support Care Cancer*. 2011;19(7):1001–1008.
15. Uys A, Rapoport BL, Anderson R. Febrile neutropenia: a prospective study to validate the Multinational Association of Supportive Care of Cancer (MASCC) risk index score. *Support Care Cancer*. 2004;12(8):555–560.
16. Kern WV, Cometta A, deBock R, et al. Oral versus intravenous empiric therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. *N Engl J Med*. 1999;341(5): 312–318.
17. Perrone J, Hollander JE, Datner EM. Emergency department evaluation of patients with fever and chemotherapy-induced neutropenia. *J Emerg Med*. 2004;27(2):115–119.
18. Ozer H, Mirtsching B, Rader M, et al. Neutropenic events in community practices reduced by first and subsequent cycle pegfilgrastim use. *Oncologist*. 2007;12(4):484–494.
19. Antoniadou A, Giamarellou H. Fever of unknown origin in febrile leukopenia. *Infect Dis Clin North Am*. 2007;21(4):1055–1090.
20. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Med*. 2008;34(1):17–60.
21. Rolston KV. Challenges in the treatment of infections caused by gram-positive and gram-negative bacteria in patients with cancer and neutropenia. *Clin Infect Dis*. 2005;40(suppl 4):s246–s252.
22. Cornetta A, Calandra T, Gaya H, et al. Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. *Antimicrobial Agents Chemotherapy*. 1996;40(5):1108–1115.
23. Pizzo PA, Hathorn JW, Hiemenz J, et al. A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. *N Engl J Med*. 1986;315(9): 552–558.
24. Klastersky J. The changing face of febrile neutropenia—from monotherapy to moulds to mucositis. Why empirical therapy? *J Antimicrob Chemother*. 2009;63(suppl 1):i14–i15.
25. Paul M, Soares Weiser K, Leibovici L. Beta lactam versus beta lactam-aminoglycoside combination therapy in cancer patients with neutropenia: systematic review and meta-analysis. *BMJ*. 2003;326(7399): 1111–1120.

26. Raad I, Escalante C, Hachem RY, et al. Treatment of febrile neutropenic patients with cancer who require hospitalization: a prospective randomized study comparing imipenem and cefepime. *Cancer*. 2003; 98(5):1039–1047.
27. Bow EJ, Rotstein C, Noskin GA, et al. A randomized, open-label, multicenter comparative study of the efficacy and safety of piperacillin-tazobactam and cefepime for the empirical treatment of febrile neutropenic episodes in patients with hematologic malignancies. *Clin Infect Dis*. 2006;43(4):447–459.
28. Yahav D, Paul M, Fraser A, Sarid N, Leibovici L. Efficacy and safety of cefepime: a systematic review and meta-analysis. *Lancet Infect Dis*. 2007;7(5):338–348.
29. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005;171(4):388–416.
30. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children: executive summary. *Clin Infect Dis*. 2011;52(3):285–292.
31. Wunderink RG, Rello J, Cammarata SK, et al. Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant Staphylococcus aureus nosocomial pneumonia. *Chest*. 2003;124(5):1789–1797.
32. Powers JH, Ross DB, Lin D, Soreth J. Linezolid and vancomycin for methicillin-resistant Staphylococcus aureus nosocomial pneumonia: the subtleties of subgroup analysis. *Chest*. 2004;126(1):314–315.
33. Pichichero ME. Cephalosporins can be prescribed safely for penicillin-allergic patients. *J Fam Pract*. 2006;55(2):106–112.
34. Sodhi M, Axtell, SS, Callahan J, Shekar R. Is it safe to use carbapenems in patients with a history of allergy to penicillin? *J Antimicrob Chemother*. 2004;54(6):1155–1157.
35. Pizzo PA. Management of fever in patients with cancer and treatment-induced neutropenia. *N Engl J Med*. 1993;328(18):1323–1332.
36. Paul M, Borok S, Fraser A, et al. Empirical antibiotics against gram-positive infections for febrile neutropenia: systematic review and meta-analysis of randomized control trials. *J Antimicrob Chemother*. 2005;55(4):436–444.
37. Klastersky J, Paesmans M, Georgala A, et al. Outpatient oral antibiotics for febrile neutropenic cancer patients using a score predictive for complications. *J Clin Oncol*. 2006;24(25):4129–4134.
38. Elting LS, Bodey GP, Keefe BH. Septicemia and shock syndrome due to viridans streptococci: a case-control study of predisposing factors. *Clin Infect Dis*. 1992;14(6):1201–1207.
39. Rolston KV, Rubenstein EB, Freifeld A. Early empiric antibiotic therapy for febrile neutropenia patients at low risk. *Infect Dis Clin North Am*. 1996;10(2):223–237.
40. Cloutier RL. Neutropenic enterocolitis. *Hematol Oncol Clin North Am*. 2010;24(3):577–584.
41. Halsey J. Current and future treatment modalities for Clostridium difficile-associated disease. *Am J Health Syst Pharm*. 2008;65(8):705–715.
42. Elting LS, Lu C, Escalante CP, et al. Outcomes and cost of outpatient and inpatient management of 712 patients with febrile neutropenia. *J Clin Oncol*. 2008;26(4):606–611.
43. Lazarus HM, Creger RJ, Gerson SL. Infectious emergencies in oncology patients. *Seminal Oncol*. 1989;16(6):543–560.
44. Bow EJ. Fluoroquinolones, antimicrobial resistance and neutropenic cancer patients. *Curr Opinion Infect Dis*. 2011;24(6):545–553.
45. Wingard JR, Eldjerou L, Leather H. Use of antibacterial prophylaxis in patients with chemotherapy-induced neutropenia. *Curr Opin Hematol*. 2012;19(1):21–26.
46. Cometta A, Calandra T, Billie J, Glauser MP. Escherichia coli resistant to flouroquinolones in patients with cancer and neutropenia. *N Engl J Med*. 1994;330(17):1240–1241.
47. Gafter-Gvili A, Paul M, Fraser A, Leibovici L. Effect of quinolone prophylaxis in afebrile neutropenic patients on microbial resistance: systematic review and meta-analysis. *J Antimicrob Chemother*. 2007;59(1):5–22.
48. Dellit TH, Owens RC, McGowan JE Jr, et al; Infectious Diseases Society of America; Society for Healthcare Epidemiology of America. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis*. 2007;44(2):159–177.
49. Bochud PY, Eggiman, P, Calandra T, Van Melle G, Saghafi L, Francioli P. Bacteremia due to viridans streptococcus in neutropenic patients with cancer: clinical spectrum and risk factors. *Clin Infect Dis*. 1994;18(1):25–31.
50. Ng ES, Liew Y, Earnest A, Koh LP, Lim SW, Hsu LY. Audit of fluoroquinolone prophylaxis against chemotherapy-induced febrile neutropenia in a hospital with highly prevalent fluoroquinolone resistance. *Leuk Lymphoma*. 2011;52(1):131–133.
51. Pitout JD, Laupland KB. Extended spectrum beta-lactamase producing Enterobacteriaceae: an emerging public health concern. *Lancet Infect Dis*. 2008;8(3):159–166.
52. Liss BJ, Vehreschild JJ, Cornely OA, et al. Intestinal colonization and blood stream infections due to vancomycin-resistant enterococci (VRE) and extended-spectrum beta-lactamase producing Enterobacteriaceae (ESBLE) in patients with haematological and oncological malignancies. *Infection*. 2012;40(6):613–619.
53. Cho SY, Choi HY. Opportunistic fungal infection among cancer patients. A ten-year autopsy study. *Am J Clin Pathol*. 1979;72(4):617–621.
54. Kibbler CC. Empirical antifungal therapy in febrile neutropenic patients: current status. *Curr Top Med Mycol*. 1997;8(1–2):5–14.
55. Wingard JR, Leather HL. Empiric antifungal therapy for the neutropenic patient. *Oncology*. 2001;15(3):351–369.
56. Klastersky J. Antifungal therapy in patients with fever and neutropenia—more rational and less empirical? *N Engl J Med*. 2004;351(14): 1445–1447.
57. Walsh TJ, Finberg RW, Arndt C, et al; National Institute of Allergy and Infectious Diseases Mycoses Study Group. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. *N Engl J Med*. 1999;340(10):764–771.
58. Walsh TJ, Teppler H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med*. 2004;351(14):1391–1402.
59. Pappas PG, Kauffman CA, Andes D, et al; Infectious Diseases Society of America. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48(5):503–535.
60. Segal BH, Almyroudis NG, Battiwala M, et al. Prevention and early treatment of invasive fungal infection in patients with cancer and neutropenia and in stem cell transplant recipients in the era of newer broad-spectrum antifungal agents and diagnostic adjuncts. *Clin Infect Dis*. 2007;44(3):402–409.
61. Walsh TJ, Anaisse EJ, Denning DW, et al; Infectious Diseases Society of America. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;46(3):327–360.
62. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. *Clin Infect Dis*. 2008;46(2):201–211.
63. Boutati EI, Anaisse EJ. Fusarium, a significant emerging pathogen in patients with hematologic malignancy: ten years' experience at a cancer center and implications for management. *Blood*. 1997;90(3):999–1008.
64. Perfect JR, Marr KA, Walsh TJ, et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. *Clin Infect Dis*. 2003;36(9):1122–1131.
65. Raad II, Hachem RY, Herbrecht R, et al. Posaconazole as salvage treatment for invasive fusariosis in patients with underlying hematologic malignancy and other conditions. *Clin Infect Dis*. 2006;42(10):1398–1403.
66. Perfect JR. Treatment of non-Aspergillus moulds in immunocompromised patients, with amphotericin B lipid complex. *Clin Infect Dis*. 2005;40(suppl 6):S401–S408.

67. Cuenca-Estrella M, Gomez-Lopez A, Mellado E, Buitrago MJ, Monzon A, Rodriguez-Tudela JL. Head-to-head comparison of the activities of currently available antifungal agents against 3,378 Spanish clinical isolates of yeasts and filamentous fungi. *Antimicrob Agents Chemother*. 2006;50(3):917–921.
68. Espinel-Ingroff A, Johnson E, Hockey H, Troke P. Activities of voriconazole, itraconazole, and amphotericin B in vitro against 590 moulds from 323 patients in the voriconazole phase III clinical studies. *J Antimicrob Chemother*. 2008;61(3):616–620.
69. Senn L, Robinson JO, Schmidt S, et al. 1,3-Beta-D-glucan antigenemia for early diagnosis of invasive fungal infections in neutropenic patients with acute leukemia. *Clin Infect Dis*. 2008;46(6):878–885.
70. Mennink-Kersten MA, Donnely JP, Verweij PE. Detection of circulating galactomannan for the diagnosis and management of invasive aspergillosis. *Lancet Infect Dis*. 2004;4(6):349–357.
71. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. *Clin Infect Dis*. 2006;42(10): 1417–1427.
72. Cordonnier C, Pautas C, Maury S, et al. Empirical versus pre-emptive antifungal therapy for high-risk febrile neutropenic patients: a randomized, controlled trial. *Clin Infect Dis*. 2009;48(8):1042–1051.
73. Fowler VG Jr, Sanders LL, Sexton DJ, et al. Outcome of Staphyloccus aureus bacteremia according to compliance with recommendations of infectious diseases specialists: experience with 244 patients. *Clin Infect Dis*. 1998;27(3):478–486.
74. Hanna H, Afif C, Alakech B, et al. Central venous catheter-related bacteremia due to gram-negative bacilli: significance of catheter removal in preventing relapse. *Infect Control Hosp Epidemiol*. 2004;25(8):646–649.
75. Raad I, Hanna H, Boktor M, et al. Management of central venous catheters in patients with cancer and candidemia. *Clin Infect Dis*. 2004;38(8):1119–1127.
76. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence based clinical practice guideline. *J Clin Oncol*. 2006;24(19): 3187–3205.
77. Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumors. *Eur J Cancer*. 2011;47(1):8–32.

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