clinical review

Optimal Management of Neutropenic Fever in Patients With Cancer

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abstract

Febrile neutropenia remains an important complication of treatment with cytotoxic chemotherapy. It is often the first and sometimes the only sign or symptom of infection in this vulnerable patient population. Urgent and appropriate evaluation and treatment are imperative because delay in initiating appropriate antibiotic therapy may be life threatening. Selection of antibiotics should be based on the patient's symptoms, previous culture data, and institutional antibiograms. Ongoing therapy should be guided by culture and clinical data. Antimicrobial resistance is of great concern, particularly in this population, so careful attention to antibiotic selection and duration is needed.

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BACKGROUND

Neutrophils play an essential role in the innate immune system by responding to invading pathogens by directly attacking bacterial cells or fungal hyphae and releasing cytokines to recruit inflammatory responses at the site of infection. Therefore, quantitative or qualitative deficits in neutrophils put a patient at risk for infections caused by bacterial and fungal organisms, in particular. Many cytotoxic chemotherapy agents act on the myeloproliferative cells of the bone marrow, in addition to their intended tumor cell targets, resulting in neutropenia. These agents also damage rapidly dividing cells; of particular concern are those cells lining gut mucosa because these cells act as an anatomic barrier to the bacterial organisms that colonize the GI tract. Therefore, patients receiving cytotoxic chemotherapy for malignancy are at high risk for infection-related complications, particularly caused by bacterial and fungal organisms. The degree and duration of neutropenia directly correlate with risk for infection; this relationship was initially described in patients with acute myeloid leukemia by Bodey et al[1] in 1966. In addition to increased risk for infection, patients with neutropenia often have more subtle or delayed signs or symptoms of localized infection as a result of the inability to mount an inflammatory response. In fact, febrile neutropenia may be the only sign of infection in this population. Therefore, febrile neutropenia requires urgent and thorough evaluation and treatment.

DEFINITIONS AND EPIDEMIOLOGY

Febrile neutropenia is defined as a one-time oral temperature of greater than 38.3°C (approximately 100.9°F) or a sustained temperature of greater than 38°C (100.4°F) for ≥ 1 hour in a patient who has an absolute neutrophil count of less than 500 cells/μL or an absolute neutrophil count expected to decrease to less than 500 cells/μL within a 48-hour period.[2] Typically, the onset of neutropenia occurs approximately 1 week after delivery of cytotoxic chemotherapy. Patients receiving chemotherapy for solid tumors will generally have neutropenia that lasts less than 7 days, and only 5% to 30% will have febrile neutropenia, with the highest rates occurring during the first cycle of treatment. Conversely, patients undergoing hematopoietic stem-cell transplantation with conditioning therapy or receiving chemotherapy for hematologic malignancies have more prolonged neutropenia that may last 14 days or more. Consequently, more than 80% of patients receiving chemotherapy for leukemia or undergoing allogeneic hematopoietic stem-cell transplantation will experience at least one episode of febrile neutropenia.[2-5]

An infectious etiology is only identified in 40% to 50% of neutropenic fevers, with 10% to 30% having bacteremia.[3-5] Nonetheless, all patients presenting with febrile neutropenia require empiric antibiotic coverage urgently. This is because there are no specific tests or scoring systems to reliably distinguish patients who have bacteremia from those who are uninfected. Accordingly, all patients must be given the benefit of initial empiric therapy that primarily covers the gram-negative pathogens that represent the greatest threat to them.[2,6]

The most common source of bacteremia in this population is from translocation of enteric bacteria into

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the bloodstream. Catheter-related bloodstream infections are also an important cause of infection in patients with febrile neutropenia, and it has historically been difficult to identify bacteremias caused by catheters versus those that originated from the gut. Recently, the National Healthcare Safety Network developed a new surveillance definition of mucosal barrier injury–associated laboratory-confirmed bloodstream infection to distinguish bloodstream infections caused by oral or intestinal microbiota in patients with cancer from those that are catheter related and thus improve the comparability of central line–associated bloodstream infection rates at cancer and noncancer centers. These definitions apply to patients who are neutropenic or who have undergone transplantation who have a bloodstream infection caused by an organism that is known to colonize the GI tract.[7] Upon application of these definitions, many bloodstream infections that were previously attributed to being catheter related have been reclassified as mucosal barrier injury–associated laboratory-confirmed bloodstream infections.[8]

The gram-negative rods, particularly Enterobacteriaceae (including *Escherichia coli*, *Klebsiella* species, and *Enterobacter* species) and *Pseudomonas aeruginosa*, are historically the most common pathogens causing bloodstream infections in neutropenic patients with cancer, but more recently, gram-positive organisms, such as coagulase-negative staphylococci and viridans group streptococci, have become more prevalent. However, because of the high morbidity and mortality associated with gram-negative sepsis, empiric therapy for febrile neutropenia should target these organisms specifically. In the absence of adequate neutrophil numbers in circulation, unopposed gram-negative bacteremia has a mortality rate of up to 70% in neutropenic patients who do not receive empiric antibiotics.[9,10] In contrast, various studies have shown the overall mortality rate to be 4% to 20% in patients with neutropenic fever who are treated with empiric antibiotic therapies, with higher mortality seen in patients with multiple comorbidities, documented gram-negative rod bacteremia, and/or tissue-invasive infections such as pneumonia.[11]

The underlying malignancy and the cumulative treatment also influence the risk and spectrum of infection. Patients with refractory disease who have received multiple lines of chemotherapy and have had more prolonged neutropenia are typically at higher risk for infectious complications compared with patients who are earlier in their treatment course. Tumors that obstruct lumens or invade contaminated sites (especially bowel) are also potential sources of infection.

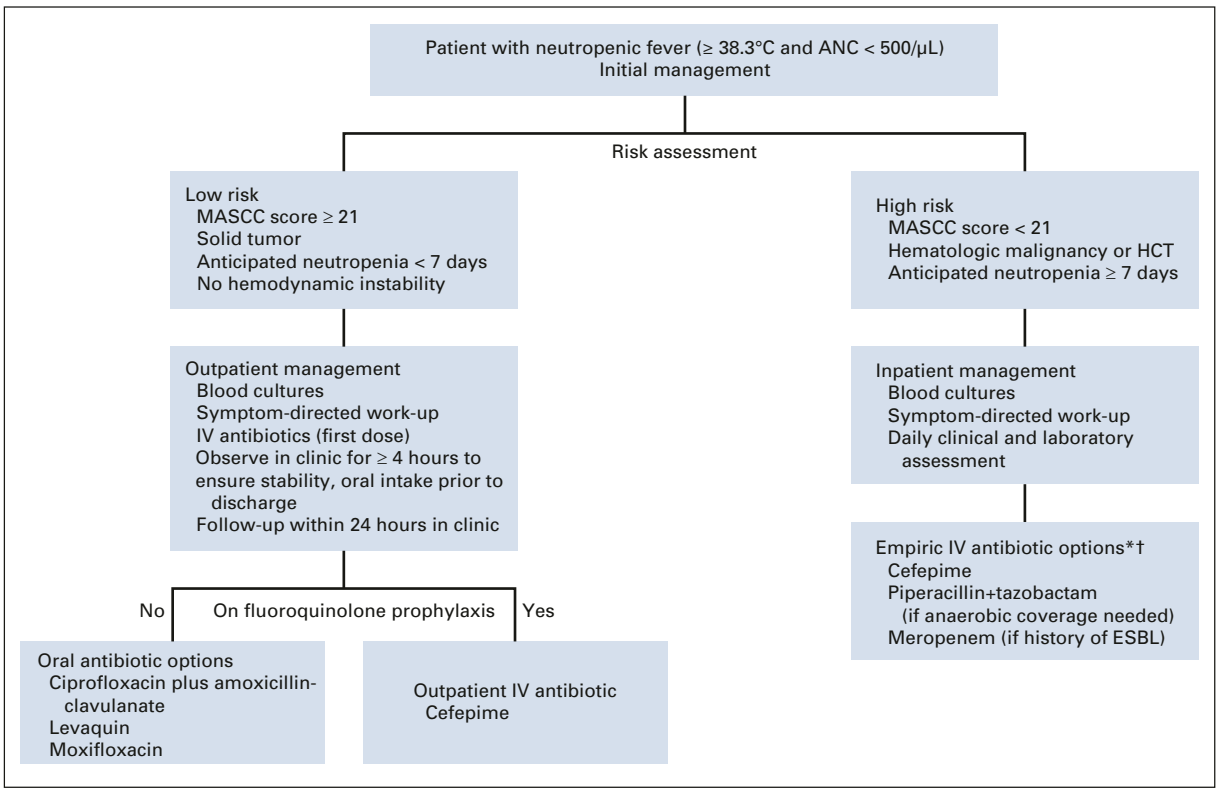

FIG 1. Flowchart of patient with neutropenic fever.[2] (*) Based on institutional antibiogram. (†) Indications to add vancomycin include hemodynamic instability, skin or catheter site infection, concern for methicillin-resistant *Staphylococcus aureus* pneumonia, and blood cultures with gram-positive bacteria before final identification and susceptibilities. ANC, absolute neutrophil count; ESBL, extended-spectrum β-lactamase; HCT, hematopoietic cell transplantation; IV, intravenous; MASCC, Multinational Association for Supportive Care in Cancer.

INITIAL EVALUATION

Patients presenting with febrile neutropenia should be have at least two sets of blood cultures obtained, ideally one from a peripheral venipuncture and one from a central venous catheter, if present, followed by empiric antibiotics (regimens discussed later). The patient should undergo a detailed history and physical examination (Fig 1). Important factors to consider in the history include comprehensive review of systems, medical comorbidities, chemotherapy regimen and timing from most recent chemotherapy cycle, prior infections, recent antibiotic prophylaxis or therapy, potential ill contacts, and social history. The physical examination should include special attention to the skin, catheter sites, lungs, sinuses, mouth, abdomen, perirectal area, and neurologic system as potential sources for infections in patients with neutropenia caused by chemotherapy. Routine laboratory tests should be performed, including CBC with differential and comprehensive metabolic panel, in addition to symptom-directed work-up with cultures and/or imaging. For example, patients with respiratory symptoms should have a chest radiograph or computed tomography scan and sputum culture (if feasible) and should be considered for respiratory viral testing, particularly during influenza season.

RISK ASSESSMENT

The Multinational Association for Supportive Care in Cancer (MASCC) risk index score was published in 2000 with a goal of identifying patients who, on presentation with febrile neutropenia, are at low risk for mortality and other serious complications during the subsequent course of neutropenia.[12] With early identification of those at low versus high risk for complications, it is possible to develop less intensive empiric antibiotic management schemes for the low-risk group (ie, oral and/or outpatient antibiotics). The factors that compose this weighted MASCC scoring system include degree of symptoms attributable to febrile neutropenia at presentation, hypotension, history of pulmonary disease, history of fungal infection, dehydration, age, and whether the patient is an outpatient or inpatient at the time of onset of febrile neutropenia (Table 1).[12,13] This algorithm has been validated by numerous studies, with sensitivities and specificities ranging from 71% to 95% and 40% to 95%, respectively. Patients with a MASCC score of 21 or more who are considered to be low risk for complications related to febrile neutropenia may be considered for outpatient management after initial evaluation if they live within an hour of the medical center, have a caregiver at home, and are able to return (quickly if necessary) to the medical center for emergency or follow-up care.

INITIAL EMPIRIC THERAPY

Patients with a high MASCC score and thus deemed to be low risk who are planned to be treated as outpatients are usually given a dose of intravenous antibiotics after blood cultures are obtained. Then they may be treated with an oral regimen such as ciprofloxacin plus amoxicillin-clavulanic acid, levofloxacin, or moxifloxacin.[6,14] Alternatively, patients may also continue the intravenous antibiotic, to be administered at home or in an outpatient setting. Patients should be evaluated daily in the first 72 hours and should also be counseled to return if blood cultures become positive, they develop new signs or symptoms, or they have persistent or recurrent fever after 3 to 5 days (Fig 2). Of note, patients who are already receiving an oral fluoroquinolone as prophylaxis are not candidates for treatment with oral agents.[15]

Patients with fever and neutropenia who do not meet the aforementioned low-risk MASCC criteria, with a score of less than 21 points, are considered to be at high risk for complications during their ensuing course of neutropenia.[12] Although duration of neutropenia is not included as a risk factor in the MASCC scoring system, it is our practice to admit all patients who are receiving chemotherapy, especially for acute myelogenous leukemia, or stem-cell transplantation, and are expected to have more than a week of low absolute neutrophil counts (< 500 cells/μL). High-risk patients should be admitted to the hospital for evaluation and treatment of potential infection. This process should take no more than 1 hour from presentation to receipt of antibiotics because delays are associated with worse outcomes.[16] Patients should receive immediate treatment with a broad-spectrum parenteral antibiotic that has antipseudomonal activity. The following two management strategies have been outlined for the treatment of these patients: escalation and de-escalation.[17] The de-escalation approach includes initial multiagent therapy that includes coverage for multidrug-resistant gram-negative

TABLE 1. The Multinational Association for Supportive Care in Cancer (MASCC) Score

Characteristic	Weight
Burden of febrile neutropenia	
No or mild symptoms	5
Moderate symptoms	3
No hypotension (SBP > 90 mm Hg)	5
No active COPD	4
Solid tumor or no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Outpatient status	3
Age < 60 years	2

NOTE. Applicable points are added to create a cumulative score. The maximum score is 26, and a score of greater than 20 has a predicted low risk (< 10%) for serious medical complications during the course of the febrile neutropenia.[13]

Abbreviations: COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure.

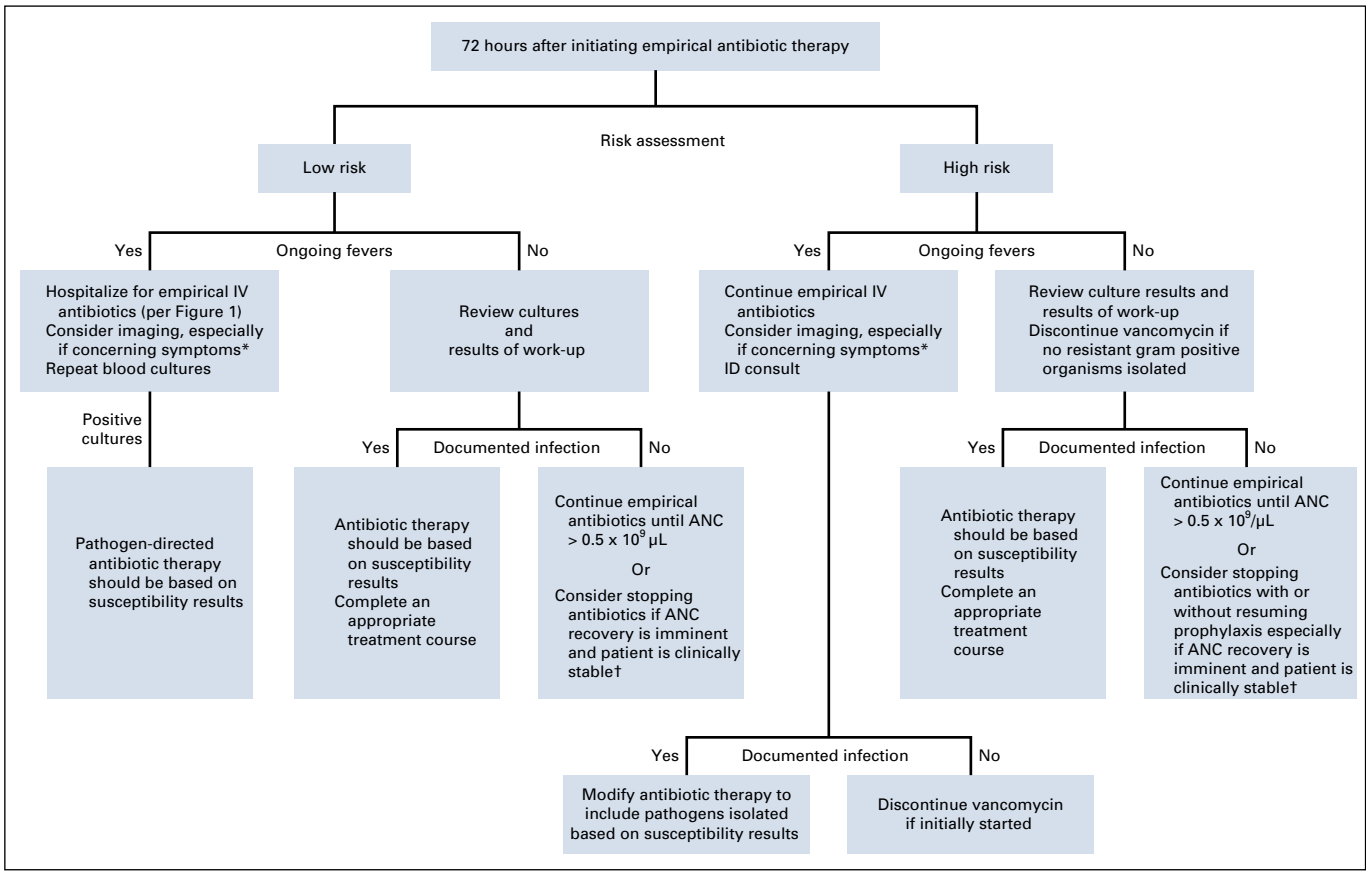

FIG 2. Flowchart of risk assessment 72 hours after initiating empirical antibiotic therapy.[2,17] (*) Imaging may include computed tomography of the sinuses, chest, abdomen, and/or pelvis depending on symptoms and severity of illness. (†) This practice is controversial, and more clinical trial data are needed, but European Conference on Infections in Leukaemia guidelines support this option. ANC, absolute neutrophil count; ID, infectious disease; IV, intravenous.

rods and gram-positive cocci (eg, carbapenem in combination with an aminoglycoside and glycopeptide). This broad-spectrum therapy is typically reserved for patients who present with severe sepsis or who are known to be colonized with resistant bacteria. Once the patient is improving and cultures are negative for a multidrug-resistant organism, treatment can be de-escalated to more narrow coverage. Alternatively, patients with febrile neutropenia who are stable at presentation are typically treated with the escalation approach with β-lactam monotherapy initially with addition of agents if indicated on the basis of culture data or clinical detoriation.[17] Agents that are widely recommended and proven efficacious include cefepime, piperacillin-tazobactam, ceftazidime, or an antipseudomonal carbapenem (imipenem or meropenem).[2,6] The choice of monotherapy should be guided by previous infections and susceptibility patterns as well as institutional antibiograms. Symptoms, complaints, and physical examination findings are important considerations when choosing therapy. For example, patients with abdominal symptoms such as abdominal pain or diarrhea may also need anaerobic coverage with the preferential use of piperacillin-tazobactam as initial empiric therapy or the addition of metronidazole to cefepime. Although the antipseudomonal carbapenems have excellent antianaerobic activity, they are best reserved for use in treating complicated infections with drug-resistant organisms such as extended-spectrum β-lactamase–producing Enterobacteriaceae. Depending on site antibiogram profiles showing carbapenem coverage of most gram-negative pathogens, carbapenems may be a good choice for neutropenic patients presenting with sepsis. Carbapenems are not recommended for routine coverage in uncomplicated, stable patients.

The use of fluoroquinolone prophylaxis has reduced the rates of infections due to gram-negative rods.[18] However, fluoroquinolones are commonly associated with increased rates of multidrug-resistant organisms, thus placing patients at risk for breakthrough infections that may be less amenable to antibiotic treatment. In addition, most studies do not demonstrate an improvement in overall survival with the use of prophylaxis, so prophylaxis varies according to center. In centers at which fluoroquinolone prophylaxis is used, vigilance for multidrug-resistant organisms needs to be high.

Although gram-positive bacteremias have become more common in the past 30 years, they rarely cause rapid demise in patients with febrile neutropenia, with the exception of

viridans group streptococci. Accordingly, for stable patients without sepsis, pneumonia, mucositis, or evidence of line infection, there is no benefit to empirically adding vancomycin to the initial empiric regimen used for management of neutropenic fever.[19,20] Several clinical practice guidelines exist to help with management of febrile neutropenia.[2,7,21]

ONGOING MANAGEMENT OF FEBRILE NEUTROPENIA

Patients with neutropenic fever should be examined daily with attention to fever curve and new signs or symptoms. If at any point in the patient's course, the patient becomes hemodynamically unstable or develops other signs of sepsis, therapy should immediately be broadened to include coverage against resistant gram-negative rods, gram-positive cocci, and anaerobes as well as *Candida*. Additional work-up should also be performed, including repeating physical examination, blood cultures, and imaging. Strong consideration should be given to consulting an infectious diseases specialist to help guide work-up and treatment if not already done.

In patients who are stable but have ongoing fevers despite more than 3 to 4 days of treatment with broad-spectrum antibiotics without an identified source, there is no need to broaden antibiotic therapy. Fever alone in an otherwise stable patient is not an indication to add or change antimicrobials. However, additional work-up may be indicated in patients with new or persistent fever during neutropenia. Thorough review of systems and physical examinations focused on skin (including catheter exit sites), lungs, abdomen, and any areas about which the patient expresses concern are in order. In addition, high-risk patients with hematologic malignancies who are anticipated to have neutropenia for greater than 7 days should be closely evaluated for invasive fungal disease and may require computed tomography scans of the sinuses, chest or abdomen, and pelvis depending on symptoms. Fungal markers including galactomannan and 1,3-β-D-glucan can be sent for evaluation, but it should be noted that the sensitivities of these two tests are only 49% to 80% and 40% to 90%, respectively.[22-24] Both markers are usually negative in the setting of mucormycosis. Therefore, empiric antifungal therapy should also be a consideration, especially in patients with acute leukemia, patients receiving allogeneic hematopoietic stem-cell transplantation, or patients receiving high-dose corticosteroids who are at high risk for mold infections.

If a bacterial pathogen is identified via cultures, once these patients defervesce and are stable, de-escalating to narrower, targeted therapy can be considered. For example, if a patient has a bloodstream infection as a result of a sensitive *E coli* organism and no *P aeruginosa* is present, the patient can be switched to ceftriaxone for the duration of treatment provided that he or she remains stable and afebrile. Whether patients need to be continued on this therapy throughout the duration of their neutropenia is controversial.

Practices vary among centers and in the guidelines if no infectious etiology is identified. The European Conference on Infections in Leukaemia guidelines suggest stopping broad-spectrum antibiotic therapy and/or resuming prophylaxis. Conversely, the Infectious Diseases Society of America and National Comprehensive Cancer Network favor the continuation of broad-spectrum therapy until recovery of neutrophils. However, in a recent multicenter study conducted in Spain, patients with hematologic malignancies with neutropenic fevers and negative blood cultures were randomly assigned to either continuation of empiric antibiotics or cessation of antibiotics after being afebrile for 72 hours. Cumulative days of antibiotic therapy were lower in the group with early de-escalation, and adverse events, including recurrent fevers and infections, were similar between the two groups.[25] Although we anticipate that more data on this topic will be forthcoming, this study suggests that cessation of antibiotics before neutrophil recovery in stable afebrile patients without an identified infection may be a reasonable approach.

The management of febrile neutropenia requires urgent evaluation and medical attention with administration of antibiotics within 1 hour of presentation. It is important to have a working knowledge of site-specific susceptibility patterns and to pay attention to the patient's specific history and symptoms, which may give clues to resistant pathogens. Empiric antibiotics are standard of care and significantly reduce morbidity and mortality in patients with cancer with febrile neutropenia.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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