Neutropenic Fever

Lindsey White, MD[a],*, Michael Ybarra, MD[b]

KEY POINTS

- Neutropenic fever is an oncologic/hematologic emergency that may be encountered in the emergency department setting.
- Engaging patients' hematologist/oncologist in disposition decision making is of critical importance to managing patients with febrile neutropenia.
- Factors such as chemotherapeutic regimen, history of stem cell transplant, and cancer type place patients at varying levels of risk for serious infection.
- Neutropenic fever should trigger the initiation of rapid work-up and the administration of empiric systemic antibiotic therapy.

INTRODUCTION

Fever is a common presenting complaint among adult or pediatric patients in the emergency department (ED) setting. Although fever in healthy individuals does not necessarily indicate severe illness, fever in patients with neutropenia may herald life-threatening infection. Therefore, prompt recognition of patients with neutropenic fever is imperative. Serious bacterial illness is a significant cause of morbidity and mortality for neutropenic patients.[1] Neutropenic fever should trigger the initiation of a rapid work-up and administration of empiric systemic antibiotic therapy to attenuate or avoid the progression along the spectrum of sepsis, severe sepsis, septic shock syndrome, and death.[1]

Patients at risk for the development of neutropenic fever include patients using chemotherapeutic agents or other medications that alter immune function; patients with infections, such as human immunodeficiency virus (HIV); or individuals with other underlying immune deficiency states (congenital or acquired).

Fever may be the only presenting sign of infection. In the absence of fever, other potential signs of infection include vital sign alterations or evidence of new organ dysfunction. Emergency physicians should be aware of the infection risks, diagnostic

methods, and antimicrobial agents required for appropriate management of febrile neutropenia. The initial clinical evaluation focuses on assessing the risk of serious complications. This risk assessment determines the approach to therapy, including the need for inpatient admission and intravenous (IV) antibiotics. Therefore, algorithms for evaluation, diagnosis, and prophylactic treatment have been developed.

DEFINITIONS

The Infectious Disease Society of America (IDSA) defines fever in neutropenic patients as a single oral temperature of greater than 38.0°C, or 100.4°F, for greater than 1 hour.[2] Although rectal measurement most accurately reflects the core body temperature, oral or axillary temperature measurements are recommended because of the theoretical risk of bacterial translocation during the procedure of inserting the thermometer probe into the anus.

Although the definition of neutropenia varies from institution to institution, neutropenia is typically defined as an absolute neutrophil count (ANC) of less than 1500 cells per microliter.[2] Severe neutropenia is defined as an ANC less than 500 cells per microliter or an ANC that is expected to decrease to less than 500 cells per microliter over the next 48 hours.[2] Neutropenia can be further categorized as mild, moderate, or severe. Mild neutropenia is defined as an ANC between 1000 and 1500 cells per microliter. Moderate neutropenia is defined by an ANC between 500 and 1000 cells per microliter, and severe neutropenia is defined as an ANC less than 500 cells per microliter. This classification is depicted in **Table 1**.

Because the risk of clinically significant infection increases as the neutrophil count decreases to less than 500 cells per microliter,[3] for the purposes of the discussion that follows, the authors *define neutropenia as an ANC less than 500* cells per microliter. Furthermore, the risk of clinically significant infection is higher in those with a prolonged duration of neutropenia (more than 7 days).[2] There is an inverse relationship between mortality associated with febrile neutropenia and the absolute neutrophil count.[4]

Although some laboratories report a calculated ANC, it is important for the emergency physician to know how to calculate the ANC. The ANC can be calculated by multiplying the total white blood cell (WBC) count by the percentage of polymorphonuclear cells and bands (**Table 2**).

For example, in a patient with the following complete blood count (CBC), the ANC is equal to 2000 cells per microliter $\times$ (10% neutrophils + 15% bands) = 2000 $\times$ 25% = 500 cells per microliter.

When the ANC count decreases to less than 500 cells per microliter, there is impairment in control of normal microflora of the mouth and gut.[5] In addition, acute development of neutropenia is associated with a higher risk of infection than chronic neutropenia that results over months to years. The mortality from uncontrolled

Table 1 Neutropenia classification	
Degree of Neutropenia	**ANC (cells per microliter)**
Mild	1000–1500
Moderate	500–999
Severe	<500

Data 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.

Table 2	
Sample ANC calculation	
Total Peripheral WBC Count	**WBC Count Differential (%)**
2000 cells per microliter	Neutrophils 10 Lymphocytes 50 Monocytes 25 Bands 15

infection varies inversely with the neutrophil count. If the nadir is greater 1000 cells per microliter, there is little mortality risk; if there are less than 500 cells per microliter, the risk of death is markedly increased. Neutrophils are the first-line defense against infection as the initial cellular component of the inflammatory response and a key component of innate immunity. Fever occurs in up to one-third of neutropenic episodes in certain populations.[5]

CAUSES

There are numerous potential causes that may contribute to the development of neutropenia. The most common cause of neutropenia is medications, specifically chemotherapeutic agents. Other causes are congenital, infectious, and rheumatologic. Individuals can have a genetic predisposition to neutropenia, as in Cohen syndrome. Neutropenia can also result from increased neutrophil destruction, as in autoimmune or drug-induced neutropenia.[5] The causes of neutropenia with examples are listed in **Boxes 1** and **2**.

Neutropenia is caused by medications through direct and indirect mechanisms. Neutropenia can be caused by the cytotoxic or immunosuppressive mechanisms related to the particular chemotherapy or antiretroviral agent or antibiotic. These drugs

---

Box 1
Neutropenia causes

1. Medications
   a. Chemotherapeutic agents
   b. Psychotropic drugs: clozapine, olanzapine
   c. Anticonvulsants: phenytoin, valproic acid
   d. H_2 blockers: cimetidine, ranitidine
   e. Antibiotics: penicillin, trimethoprim-sulfamethoxazole
   f. Diuretics: acetazolamide, hydrochlorothiazide
   g. Thionamides: propylthiouracil, methimazole
   h. Rheumatologic agents: rituximab, sulfasalazine
   i. Miscellaneous: nonsteroidal antiinflammatory drugs, allopurinol

2. Infectious
   a. Viral: HIV, influenza, hepatitis B, respiratory syncytial virus, cytomegalovirus
   b. Bacterial: tuberculosis, *Shigella*

3. Immune
   a. Autoimmune: chronic benign neutropenia
   b. Alloimmune: neonatal alloimmune neutropenia

4. Nutritional
   a. B_{12} or folate deficiency

Data from Harrisons. 352–353.

<div style="border:1px solid black; padding:10px;">

Box 2
Hereditary causes of neutropenia

Cohen syndrome
  An inherited disorder that affects many parts of the body and is characterized by developmental delay, intellectual disability, microcephaly, hypotonia, and in some cases neutropenia

Cyclic neutropenia
  A congenital disorder characterized by recurrent episodes of neutropenia

Kostmann syndrome
  A rare autosomal recessive form of severe chronic neutropenia usually detected soon after birth

Barth syndrome
  An X-linked genetic disorder that affects multiple body systems and may include severe neutropenia

Chediak-Higashi syndrome
  A congenital syndrome that affects many parts of the body, particularly the immune system

Data from Harrisons. 352–353.

</div>

result in either decreased production of rapidly growing progenitor cells or inhibiting proliferation of myeloid precursors to adversely affect hematopoiesis.[6] This effect is often dose related and depends on continued administration of the drug. Conversely, certain drugs cause neutropenia indirectly by serving as immune haptens, leading to immune-mediated destruction of granulocytes, including neutrophils.

Several antirheumatic medications cause both neutropenia and leukopenia; therefore, fever in patients with rheumatologic disease on therapy should be similarly evaluated. Additionally, certain medical conditions, such as Crohn disease, HIV, rheumatoid arthritis, and lupus, increase the risk of neutropenia because of increased neutrophil destruction caused by the disease process itself.

Because patients who are receiving chemotherapy experience frequent episodes of neutropenia, many studies on neutropenic fever and serious bacterial infection focus on this population. The high-risk period for the development of neutropenia is 7 to 10 days after the last chemotherapeutic dose and up to 5 days thereafter. The lowest neutrophil count is typically 5 to 10 days after the last dose, and recovery is typically 5 days later.[7]

The type of chemotherapeutic agent may affect the risk for development of neutropenia, as some chemotherapy regimens are more myelotoxic than others. For example, chemotherapy regimens for solid tumors often cause neutropenia of shorter duration as compared with chemotherapy regimens for hematologic malignancies. An estimated 10% to 50% of solid tumors and more than 80% of hematologic malignancies will develop fever during at least one cycle of chemotherapy with associated neutropenia.[2] It is also important to note that expected ANC varies by race and age. The infection risk is also increased by the presence of indwelling vascular catheters, often used for chemotherapy administration; the duration of neutropenia; and other comorbid conditions.[7]

Noniatrogenic causes of neutropenia include infectious, congenital, and autoimmune. The most common causes of nonchemotherapy-related neutropenia are viral suppression and sepsis.[5] Viruses, such as Epstein-Barr virus, influenza, and cytomegalovirus, can cause neutropenia by viral-mediated bone marrow suppression.

CLINICAL SCENARIOS

The International Immunocompromised Host Society has identified the following neutropenic fever syndromes[8]:

1. Microbiologically documented infection
2. Clinically documented infection
3. Unexplained fever

Microbiologically documented infection results when patients have both fever and neutropenia as well as an identified pathogen, based on microbiologic results, that corresponds with a clinical focus of infection. This diagnosis is difficult to make in the ED given that microbiologic results, such as urine, respiratory, or blood cultures, often require at least 24 hours before preliminary results are available. This situation may, however, be encountered in the ED if a patient is evaluated by their oncologist/hematologist as an outpatient and sent to the ED after a culture result is found to be positive.

Clinically documented infection occurs when patients have fever, neutropenia, and physical signs or symptoms that indicate a possible infectious source but do not yet have a confirmed pathogen. This scenario is a more common scenario in the ED where history and physical examination findings and laboratory and radiologic studies suggest an infectious source and dictate antibiotic selection and disposition before microbiologic confirmation.

Unexplained fever is the syndrome whereby patients have both neutropenia and fever but no identified infection source suggested or identified clinically and no pathogen is identified on microbiologic studies. This clinical scenario is the most common because the incidence of clinically documented infection in febrile neutropenia is only 20% to 30%.[2]

MORTALITY

There are significant health costs associated with neutropenic fever in addition to the morbidity and mortality that affect individual patients. One study reports that mortality approaches 50% if neutropenic fever is not treated within 48 hours.[9] Mortality rates vary with the type of malignancy.[2] Hematologic malignancies, such as leukemia, typically have higher rates of mortality than solid-tumor malignancies.

Similarly, mortality rates vary with the type of infection. Infection by gram-negative organisms typically has higher mortality rates compared with gram-positive organisms.[2] A meta-analysis of antibiotic prophylaxis in neutropenic patients has demonstrated a decrease in mortality; however, there remains a significant mortality cost for neutropenic patients who develop fever.[10] In addition to increased mortality, patients with neutropenic fever are often hospitalized for significant time periods, thus increasing overall health care costs. In a multicenter trial between 1995 and 2000, Kuderer and colleagues[11] report an average length of stay of adult patients with febrile neutropenia of 11 days.

CLINICAL CONSIDERATIONS
History and Physical Examination

Fever in patients with cancer receiving chemotherapy or in patients with immune deficiency states requires prompt attention by medical professionals and an expedited work-up to evaluate for neutropenia (Fig. 1). Neutropenic fever is a medical emergency and should be treated empirically with antimicrobial therapy. Rectal
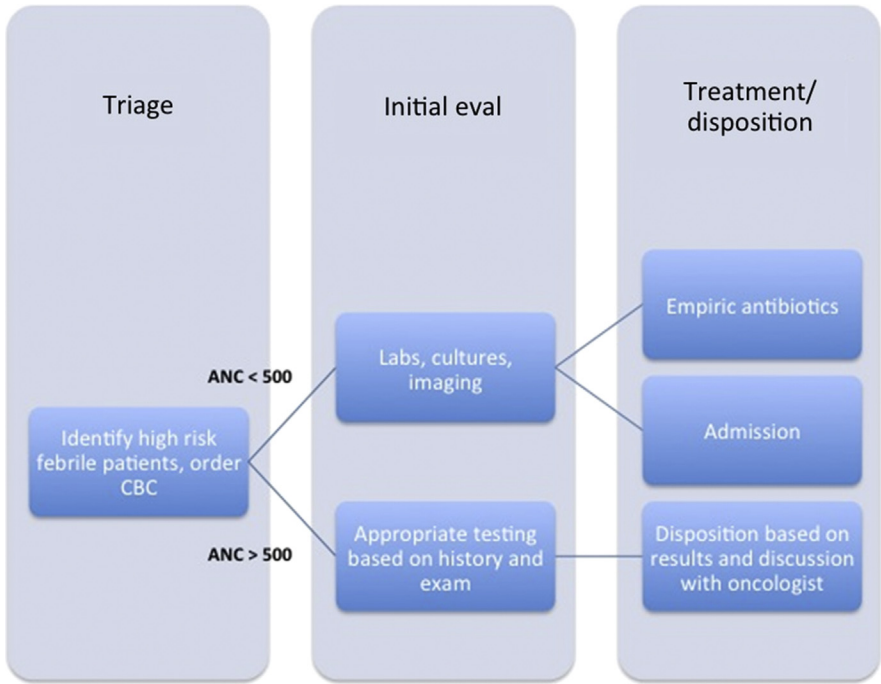
Fig. 1. Workflow for patients with febrile neutropenia.

temperatures should be avoided in neutropenic patients because of the breakdown in mucosal surfaces from cytotoxic therapy.

The key historical questions to ask include the duration and intensity of chemotherapeutic or immunosuppressive regimen, history of recent travel, presence of or exposure to animals, whether patients have been taking antimicrobial prophylaxis, and prior episodes of neutropenia or infection.

The risk of neutropenic fever in all patients receiving chemotherapy for cancer is generally low.[12] In a prospective study of 4000 patients with cancer receiving systemic chemotherapy, febrile neutropenia was documented in 14% of patients. The highest incidence followed the first cycle of chemotherapy (8%).[13] Certain chemotherapeutic regimens put patients at higher risk as does repeated cycles of chemotherapy. Cytotoxic therapy causes myelosuppression, which increases the risk of neutropenia, and epithelial damage, which increases the risk of bacterial translocation.[14] Regimens that cause mucosal damage are associated with a higher incidence of febrile events.[15]

Fever in neutropenic patients should trigger rapid evaluation, work-up, and empiric treatment. Infection is most likely to involve the integumental surfaces, such as the upper and lower respiratory tract, gastrointestinal tract, and skin.[5] Consequently, the physical examination should focus on these areas as well as vascular access points or sites of prior venipuncture.[16]

Patients may not present with typical signs and symptoms of infection. In fact, fever may be the only sign of infection in patients with neutropenia. Patients with lower ANC may lack the ability to mount an inflammatory response. Physical examination findings tend to become more muted as the ANC decreases and, therefore, may be less evident.[17] For instance, when examining the skin or soft tissues, typical findings of

infection, such as erythema, swelling, exudates, fluctuance, ulcerations, and tenderness, may be absent entirely (**Table 3**).[5,17] Similarly, pulmonary and abdominal examinations may be muted. Patients with an intra-abdominal catastrophe may not have peritonitis clinically; likewise, patients with pneumonia may not produce characteristic increased sputum or infiltrate on a routine chest radiograph.[4]

Diagnostic Testing

There are several potential causes of neutropenia as seen in **Box 1**. Emergency physicians are typically cued in to evaluating patients for neutropenic fever when they have a history of cancer or are on a chemotherapeutic medication. Patients receiving chemotherapy that present to the ED with fever should receive a diagnostic work-up to evaluate for neutropenia. However, neutropenia should be considered and ruled out in febrile patients with a history of immune deficiency or those who are taking any medication that may affect the immune system directly or indirectly.

Appropriate laboratory testing includes a CBC with differential and platelet count. Additionally, the IDSA's guidelines recommend obtaining a comprehensive metabolic panel to include electrolytes, creatinine, hepatic function, and bilirubin.[2] Blood cultures should be obtained from 2 separate sites, including one drawn from an indwelling venous catheter, if present. Cultures should be obtained if the physical examination points to additional sites of infection, such as skin cultures at sites of abscess, urine, or sputum if there is productive cough.

Patients receiving chemotherapy may not show typical signs and symptoms of respiratory and urine tract infection; therefore, a low threshold exists for ordering chest radiograph and urinalysis. The IDSA's guidelines recommend a computed tomography (CT) scan of the chest and sinuses if the fever persists after 72 hours of antibiotic therapy and there is no obvious source of infection. A CT of the chest is generally not required if a chest radiograph is negative in the ED, unless there is strong clinical suspicion for pneumonia.[5]

Stool cultures, ova and parasite, and *Clostridium difficile toxin* should be ordered in patients with diarrhea. Cultures of any sites of drainage should be obtained. If

| Table 3 | | | |
| Patient signs and symptoms | | | |
System	Patient Symptoms	Examination Findings	Diagnostic Testing
HEENT	Painful swallowing	Erythema may be faint	Consider throat culture
Respiratory	Cough	Wheezes, rales, rhonchi less common	Consider plain chest radiograph (chest radiograph) in all patients
Abdominal	Pain or tenderness	Peritoneal signs are often absent	Consider CT if patients have abdominal complaint, even if examination is benign
Skin	Pain or irritation	Erythema, induration, fluctuance can be muted	Ultrasound, or in some cases CT imaging, may be helpful to identify abscess formation
Neurologic	Headache	May lack characteristic meningismus	Consider lumbar puncture

Abbreviation: CT, computed tomography.

meningitis or encephalitis is suspected, a lumbar puncture should be performed to obtain cerebrospinal fluid. Similarly, joint aspiration should be performed if there is evidence of joint effusion or suspicion of joint infection.

Fungal cultures are generally not necessary during the initial ED evaluation. Fungal infection should be considered if the fever persists after 4 to 7 days of antibiotics or if additional diagnostic studies, such as CT of the chest and sinuses, suggest possible fungal infection.[2] Certain patients are at a higher risk for fungal infections. These patients include patients who have received allogeneic hematopoietic stem cell transplantation and intensive chemotherapy for acute myeloid leukemia, history of previous fungal infection, or are receiving total parenteral nutrition. The most common fungal pathogens are *Candida* and *Aspergillus*.[18] Similarly, empiric treatment with antiviral therapy is not indicated in the ED unless there is evidence of acute viral infection. Typical viral pathogens include herpes-simplex virus; varicella-zoster virus; cytomegalovirus; Epstein-Barr virus; and community-acquired respiratory viruses, such as respiratory syncytial virus and influenza.[19]

Antibiotic Treatment

The early administration of IV antibiotics has been shown to decrease mortality in patients with severe sepsis and septic shock.[20] Antibiotics should be initiated as soon as possible, given existing data support improved outcomes with rapid therapy.[21] Moreover, antibiotics should not be delayed because of a delay in blood or other culture acquisition.

Common bacterial pathogens are shown in **Table 4**. Bloodstream infections are typically caused by Gram-positive organisms, such as coagulase-negative *Staphylococcus*, *Staphylococcus aureus*, *Enterococcus*, *Streptococcus pneumonia*, and *Streptococcus pyogenes*; however, there are many drug-resistant gram-negative organism, such as *Escherichia coli, Klebsiella, Enterobacter*, and *Pseudomonas* infections.[22] Endogenous flora contributes to 80% of identified infections.[23]

Gram-negative bacilli, such as *Pseudomonas aeruginosa*, were predominant until the 1980s. Since the 1980s, gram-positive organisms have become the most predominant bacterial pathogens. A survey of 49 hospitals from 1995 to 2000 showed that gram-positive organisms accounted for 62% to 76% of all blood stream infections compared with only 14% to 22% for gram-negative species.[24] This transition from gram-negative to gram-positive organisms is thought to result from the increased utilization of indwelling catheters with a ready point of entry for skin flora as seen in **Fig. 2**.

Table 4 Common bacterial pathogens	
Gram-positive pathogens	Coagulase-negative *staphylococcus*, *Staphylococcus aureus* (including MRSA), *Enterococcus*, *Streptococcus viridans*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*
Gram-negative pathogens	*Escherichia coli, Klebsiella*, *Enterobacter, Pseudomonas*, *Citrobacter, Acinetobacter, Stenotrophomonas*

Abbreviation: MRSA, methicillin-resistant Staphylococcus aureus.

Data from Wisplinghoff H, Seifert H, Wenzel RP, et al. Current trends in the epidemiology of nosocomial bloodstram infections in patients with hematologic malignancies and solid neoplasms in hospitals in the United States. Clin Infect Dis 2003;36:1103; and De Pauw, Donnelly. In: Mandell, Bennett, Dolin, editors. Principles and practice of infectious diseases. 5th edition. Philadelphia: Elsevier; 2000. p. 3079–90.
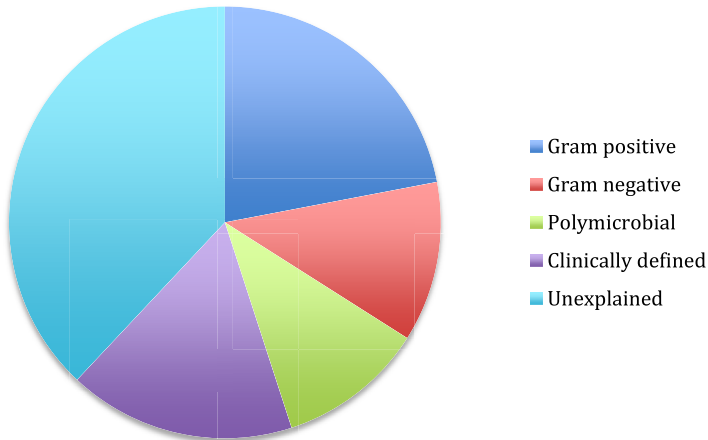
Causes of fever in neutropenic patients

- ■ Gram positive
- ■ Gram negative
- ■ Polymicrobial
- ■ Clinically defined
- ■ Unexplained

Fig. 2. Causes of fever during episodes of neutropenia. (*Data from* Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. 5th edition. Philadelphia: Elsevier, 2000;3079–90.)

First-line therapy varies based on local practice but typically includes a broad-spectrum cephalosporin with antipseudomonal activity, carbapenem, or extended-spectrum penicillin (**Table 5**). Cephalosporins are typically well tolerated in patients with penicillin allergy; but in those patients with severe allergic or anaphylactic reactions, alternative regimens include ciprofloxacin plus clindamycin or aztreonam plus vancomycin.[2]

Some physicians recommend antimicrobial prophylaxis for patients with known neutropenia. Although there is not a proven mortality benefit, patients with neutropenia for greater than 10 days are typically given a fluoroquinolone.[25] Studies demonstrate that some antibiotic prophylaxis decreases the incidence of gram-negative infections. A typical antibiotic prophylaxis regimen includes either moxifloxacin or combination therapy with ciprofloxacin and amoxicillin/clavulanic acid.[25] Currently, myeloid growth factors, empiric antiviral, or antifungal therapy are not considered part of the typical initial ED therapy.

Table 5 Empiric treatment of febrile neutropenia	
First-line therapy	Cefepime Carbapenem (meropenem or imipenem-cilastatin) Piperacillin-tazobactam
Severe penicillin allergy or complication (hypotension or pneumonia)	Aminoglycoside Fluoroquinolone
Suspected catheter-related infection, skin and soft-tissue infection, health care–associated infection, or hemodynamic instability, add extended gram-positive coverage	Vancomycin Linezolid Daptomycin

Data from 2010 IDSA guidelines. Van der Velden WJ, Blijlevens NM, Feuth T, et al. Febrile mucositis in haematopoietic sickle cell transplant recipients. Bone Marrow Transplant 2009;43(1):55–60.

Other Considerations

In order to decrease the infectious complications of neutropenia, many hematologists and oncologists use granulocyte colony-stimulating factors (such as filgrastim) or closely related granulocyte-macrophage colony-stimulating factors (such as sargramostim). They are used both as primary prophylaxis and as secondary prophylaxis in patients who became neutropenic after a previous dose of chemotherapy. Several studies have shown colony-stimulating factors decrease episodes of neutropenic fever, documented infection, and rates of hospitalization.[26]

Colony-stimulating factors have not been proven effective during episodes of neutropenic fever[17]; however, the emergency practitioner may encounter a situation whereby a patient with cancer has received a colony-stimulating factor and presents to the ED with a febrile illness. The onset of action of colony-stimulating factors is generally within 24 hours, with a peak ANC by days 3 to 5. Depending on when the colony-stimulating factor was administered, patients may present with an expected profound leukocytosis of up to 50,000/μL.[17] These patients should be worked up similarly to patients who are found to be neutropenic. Discharge can be considered in patients who clinically seem well, have no obvious source of infection after ED evaluation, and are both reliable and have close follow-up. This decision should be made in consultation with the patients' hematologist/oncologist.

Risk Stratification

The IDSA's most recent guidelines on neutropenic fever aid the clinician in risk stratifying patients (**Table 6**).[2]

There are several scoring systems developed to aid in risk stratification, including the Multinational Association for Supportive Care in Cancer (MASCC) score. The MASCC score calculates the risk based on several objective findings, such as low blood pressure, active chronic obstructive pulmonary disease, solid tumor, previous fungal infection, dehydration requiring IV fluids, clinical setting at onset of fever, and age, and one subjective component (burden of illness as reported by patients).[26] The MASCC score has favorable sensitivity when compared with other scoring systems (**Table 7**).[27]

Additional risk stratification systems exist. The MD Anderson Cancer Center developed a classification system adopted by the National Cancer Institute and European Organization for the Research and Treatment of Cancer, but it is not statistically validated.[28]

Disposition

Most patients with febrile neutropenia are admitted to the hospital for IV antibiotics. Patients should only be discharged if they meet the low-risk criteria, the patients'

Table 6
Risk stratification for patients with neutropenic fever

High-Risk Characteristics	Low-Risk Characteristics
Prolonged neutropenia (>7 d)	Brief neutropenia anticipated
Profound neutropenia (ANC <100 cells per microliter)	
Comorbid conditions	No comorbid conditions
MASCC score <21	MASCC score ≥21

Abbreviation: MASCC, Multinational Association for Supportive Care in Cancer.

Table 7
MASCC score

Category	Points
Burden of illness: no or mild symptoms	5
No hypotension (systolic blood pressure <90 mm Hg)	5
No COPD	4
Solid tumor or no previous invasive fungal infection	4
Outpatient	3
Burden of disease: moderate symptoms	3
No dehydration	3
Aged <60 y	2

Abbreviations: COPD, chronic obstructive pulmonary disease; MASCC, Multinational Association for Supportive Care in Cancer.
Data from De Souza Viana L, Serufo JC, da Costa Rocha MO, et al. Performance of a modified MASCC index score for identifying low-risk febrile neutropenic cancer patients. Support Care Cancer 2008;16(7):841–6.

hematologist/oncologist agrees with the proposed disposition, and if rapid interval follow-up and reevaluation is ensured.[20] If patients are deemed to be low risk by their hematologist/oncologist and safe for discharge, they should receive an initial dose of IV antibiotics in the ED before discharge with a prescription for oral antibiotics at home. An observational study by Etling and colleagues[29] demonstrates that selected low-risk patients who are managed as outpatients have similar outcomes when compared with similar patients managed as inpatients.

Data from the MD Anderson Cancer Center suggests that approximately 50% of patients with febrile neutropenia were ultimately diagnosed with unexplained fever.[28] These patients are without a clinically evident site of infection and have negative cultures. Of the remaining patients, only 25% were found to have a microbiologically documented infection, and 25% had a clinically evident site of infection.[28]

Among patients admitted to the hospital for empiric antimicrobial therapy, the specific level of care will be determined by the patients' clinical status. Neutropenic precautions are typically used. Patients undergoing a hematopoietic stem cell transplant should be in a single-patient room with positive pressure and high-efficiency particulate air filters when feasible. Hand-washing protocols should be strictly observed. Standard barrier precautions are recommended.[30] The neutropenic diet is typically well-cooked foods. Lunch meats from a deli counter are avoided because of the risk of listeria, as are raw or undercooked meats and unpasteurized cheeses. Well-cleaned raw fruits and vegetables are generally acceptable.[31]

Dietary counseling is an important follow-up consideration for discharged patients and is typically coordinated by the patients' oncologist/hematologist. Additionally, patients should maintain good oral hygiene and can be instructed on home skin examinations for signs of cellulitis or vascular access site infection. Menstruating women should not use tampons. Enemas, rectal probes, and suppositories should also be avoided. Potted plants and flowers should be discouraged, as various pathogenic molds have been isolated.[30]

SUMMARY

Neutropenic fever is an oncologic/hematologic emergency that may be encountered in the ED setting. Thorough evaluation, including a detailed history, comprehensive

physical examination, and laboratory data, should be initiated promptly. Furthermore, empiric antibiotics with gram-positive and gram-negative organism coverage should be initiated swiftly.

Not all patients with neutropenic fever are at the same risk of serious bacterial infection. Factors such as chemotherapeutic regimen, history of stem cell transplant, and cancer type place patients at varying levels of risk for serious infection. There are several risk-stratification tools developed to aid in the disposition decision, although the MASCC is the most widely studied.

Engaging patients' hematologist/oncologist in disposition decision making is of critical importance to managing patients with febrile neutropenia. Most patients with neutropenic fever are admitted to the hospital and started on a broad-spectrum antibiotic regimen, such as a cephalosporin with antipseudomonal activity, although it is possible to discharge selected patients on oral antibiotics if they are considered low risk by clinical criteria and close follow-up is ensured.

REFERENCES

1. Bow EJ. Infection in neutropenic patients with cancer. Crit Care Clin 2013;29:411–41.
2. 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.
3. McCurdy MT, Tsuyoshi M, Perkins J. Oncologic emergencies, part II: neutropenic fever, tumor lysis syndrome, and hypercalcemia of malignancy, vol. 12. Nocross (GA): EB Medicine; 2010. p. 3.
4. Bodey GP, Buckley M, Sathe YS, et al. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 1966;64:328–40.
5. Van der Velden WJ, Blijlevens NM, Feuth T, et al. Febrile mucositis in haematopoietic sickle cell transplant recipients. Bone Marrow Transplant 2009;43(1):55–60.
6. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. Cancer 2004;100(2):228–37.
7. Bertuch AA, Srother D. Fever in children with chemotherapy induced neutropenia. Waltham (MA): Up to Date; 2007.
8. From the Immunocompromised Host Society. The design, analysis, and reporting of clinical trials on the empirical antibiotic management of the neutropenic patient. A consensus report. J Infect Dis 1990;161:397–401.
9. Bodey GP, Jadija L, Etling L. Pseudomonas bacteremia: retrospective analysis of 410 episodes. Arch Intern Med 1985;145:1621–9.
10. Gafter-Gvilli A, Fraser A, Paul M, et al. Meta-analysis: antibiotic prophylaxis in neutropenic fever. Ann Intern Med 2005;142:979–95.
11. Kuderer NM, et al. Cost and mortality associated with febrile neutropenia in adult cancer patients. Proc Am Soc Clin Onc 2002.
12. American Society of Clinical Oncology (ASCO) Ad Hoc Colony-Stimulating Factor Guideline Expert Panel: recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. J Clin Oncol 1994;12:2471–508.
13. Available at: http://www.oncologypractice.com/jso/journal/articles/0302s152.pdf. Accessed December 5, 2013.

14. Bow EJ, Loewen R, Cheang MS, et al. Cytotoxic therapy-induced D-xylose malabsorption and invasive infection during remission-induction therapy for acute myeloid leukemia in adults. J Clin Oncol 1997;15:2254.
15. Sonis ST, Oster G, Fuchs H, et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. J Clin Oncol 2001;19:2201–5.
16. Bow EJ. Infection in neutropenic patients with cancer. Crit Care Clin 2013;29:411–41.
17. Sickles EA, Greene WH, Wiernik PH. Clinical presentation of infection in granulocytopenic patients. Arch Intern Med 1975;135:715–9.
18. Anaissie EJ, Bodey GP, Rinaldi MG. Emerging fungal pathogens. Eur J Clin Microbiol Infect Dis 1989;8:323–30.
19. Whimbey E, Englund JA, Couch RB. Community respiratory virus infections in immunocompromised patients with cancer. Am J Med 1997;102:10–8.
20. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34(6):1589–96.
21. Zuckermann J, Moreira LB, Stoll P, et al. Compliance with a critical pathway for the management of febrile neutropenia and impact on clinical outcomes. Ann Hematol 2008;87:139–45.
22. Ramphal R. Changes in the etiology of bacteremia in febrile neutropenic patients and the susceptibilities of the currently isolated pathogens. Clin Infect Dis 2004;39(Suppl 1):S25–31.
23. Hughes WT, Armstrong D, Bodey G, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002;34:730–51.
24. Wisplinghoff H, Seifert H, Wenzel RP, et al. Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematologic malignancies and solid neoplasms in hospitals in the United States. Clin Infect Dis 2003;36:1103.
25. Engels EA, Lau J, Barza M. Efficacy of quinolone prophylaxis in neutropenic cancer patients: a meta-analysis. J Clin Oncol 1998;16:1179–87.
26. Klatersky 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;18:3038–51.
27. De Souza Viana L, Serufo JC, da Costa Rocha MO, et al. Performance of a modified MASCC index score for identifying low-risk febrile neutropenic cancer patients. Support Care Cancer 2008;16(7):841–6.
28. Kantarjian HM, Wolff RA, Koller CA. The MD Anderson manual of medical oncology. 2nd edition. Available at: www.accessmedicine.com. Accessed November 20, 2013.
29. Etling LS, Lu C, Escalante CP, et al. Outcomes and cost of outpatient or inpatient management of 712 patients with febrile neutropenia. J Clin Oncol 2008;26:606–16.
30. Centers for Disease Control and Prevention, Infectious Disease Society of America, American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep 2000;49:1–125. CE1–7.
31. Gardner A, Mattiuzzi G, Faderl S, et al. Randomized comparison of cooked and noncooked diets in patients undergoing remission induction therapy for acute myeloid leukemia. J Clin Oncol 2008;26:5684–8.