

Management of febrile neutropenia

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Management of febrile neutropenic patients requires careful assessment and treatment. At least one-half of neutropenic patients who become febrile have a documented or occult infection. Early antibiotic therapy is warranted because infections can progress rapidly in these patients. Signs and symptoms of infection are often subtle because of a lack of inflammatory response. Risk assessment is important in deciding whether the patient can be treated as an inpatient or an outpatient and whether oral or intravenous antibiotics can be used. Monotherapy with a third- or fourth-generation cephalosporin or a carbapenem has been shown to be as effective as combination therapy for uncomplicated episodes of fever in neutropenic patients. Shifts in organisms responsible for infection have been seen, with more gram-positive organisms and previously less common pathogens being seen with greater frequency. Increasingly drug-resistant organisms pose an additional challenge. Empiric antifungal therapy can be indicated for neutropenic patients who remain febrile despite broad-spectrum antibiotics, and several newer treatment options are available.

Empiric antibiotic therapy in febrile, neutropenic cancer patients became well established in the 1970s, because high mortality was seen when antibiotics were withheld until infection could be proven.¹ This approach has reduced morbidity and mortality; however, changes in organisms responsible for infection, susceptible hosts, and antimicrobials have been seen.^{2,3} A careful initial evaluation of the febrile neutropenic patient, an understanding of the potential organisms responsible for infection, risk assessment to guide therapy, and appropriate use of antimicrobials are all needed to manage these patients. Signs and symptoms of infection are often subtle in the neutropenic patient,⁴ and decisions must be made when the etiology of fever is unclear and before microbiologic data are available. Many of the concepts of managing febrile neutropenic patients remain unchanged, but recent problems faced by clinicians, such as increased drug resistance and shifts in pathogens, provide new challenges.⁵⁻⁷

Clinical features of the neutropenic host

At least one-half of febrile neutropenic patients have a documented or occult infection. At least one-fifth of patients with neutrophil counts < 100 cells/mm³ have bacteremia. Fungi can be causes of secondary infection in neutropenic patients who have received broad-spectrum antibiotics and may also cause primary infections. The primary anatomic site of infection is the gastrointestinal tract, where mu-

cosal damage from chemotherapy allows invasion of micro-organisms. Damage to the skin from invasive procedures, such as intravascular devices, similarly provides portals of entry for microbes. Common sites of documented infections include the blood-

KEY POINTS

At least one-half of neutropenic patients who become febrile have an established or occult infection.

Signs and symptoms of infection are often subtle in neutropenic patients because of a lack of inflammatory response.

More gram-positive organisms, increasingly drug-resistant pathogens, and previously uncommon organisms are now on the rise. (For more on these organisms, see www.CommunityOncology.net/journal/0309.html.)

Careful risk assessment is needed to determine whether outpatient or inpatient therapy is needed and whether oral or intravenous antibiotics are needed.

Neutrophil recovery is the most important factor in deciding when to discontinue therapy.

Newer antifungal agents, which are effective and less toxic, are available for neutropenic patients who remain febrile despite broad-spectrum antibiotics.

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Bacterial pathogens commonly implicated in neutropenic fever

Gram-positive organisms

Staphylococcal species
Coagulase-negative staphylococci
Staphylococcus aureus
Streptococcal species
Viridans group
Streptococcus pneumoniae
Streptococcus pyogenes
Enterococcal species
Corynebacterium species

Gram-negative organisms

Escherichia coli
Klebsiella species
Pseudomonas aeruginosa
Enterobacter species
Acinetobacter species
Stenotrophomonas maltophilia
Non-aeruginosa *Pseudomonas* species

*More on these organisms can be found at www.CommunityOncology.net/journal/0309.

stream (15%–20%), the gastrointestinal tract (enterocolitis and perirectal infection), integument (skin and soft tissue, vascular access sites, catheter insertion sites), and the respiratory tract (sinusitis and pneumonia).

Fever

A fever can be defined as a single oral temperature $\geq 38.3^{\circ}\text{C}$ or 101°F or a temperature of $\geq 38^{\circ}\text{C}$ or 100.4°F for at least 1 hour.⁸

Neutropenia

Neutropenia can be defined as an absolute neutrophil count (ANC) < 500 cells/ mm^3 or an ANC $< 1,000$ cells/ mm^3 with a predicted decline to < 500 cells/ mm^3 . The infection rate and severity are inversely related to the ANC.^{9–11} Lower ANCs are associated with more frequent and severe infections, and conversely, higher ANCs correlate with less frequent and severe infections. Patients with neutrophil counts < 500 cells/ mm^3 are at significantly increased risk for infection compared with those with counts $< 1,000$ cells/ mm^3 ; similarly, patients with counts < 100 cells/ mm^3 are at even greater risk for infection than are those

with counts < 500 cells/ mm^3 . The duration of neutropenia is also an important determinant of risk of infection. Patients with a low ANC and prolonged neutropenia (eg, > 10 days) are at further increased risk of infection.^{9,12}

Initial evaluation

A thorough history is extremely important when evaluating patients for febrile neutropenia. The history should include the nature of the chemotherapy given, prior antibiotic prophylaxis, concomitant steroids or other immunosuppressives, recent documented colonization or infection with susceptibilities, recent surgical procedures, and medication allergies.

In neutropenic patients, symptoms and signs of inflammation may be minimal or absent.⁴ The lack of inflammatory response can make detection of infection more difficult and requires close physical examination for more subtle signs and symptoms. There will likely be decreased erythema, induration, and purulence in response to bacterial infections (eg, a skin infection without typical features of cellulitis, a pulmonary infection without a clear infiltrate, meningitis that lacks cerebrospinal fluid pleocytosis, and urinary tract infections without pyuria). Careful evaluation of common sites of infections should include the mouth, pharynx, esophagus, lungs, perineum, eyes, skin, and vascular catheter access sites.

Laboratory studies include measurement of complete blood counts, serum creatinine levels, blood urea nitrogen, transaminase levels, and blood cultures. Blood cultures should be obtained from a peripheral vein and catheter if present.¹³ Depending on the clinical situation, other cultures can be obtained. Skin biopsies can also be obtained if indicated. If respiratory signs or symptoms are present, a chest x-ray can be performed.

Risk assessment

Risk assessment is important in

deciding whether febrile neutropenic patients can be treated as inpatients or outpatients and whether oral or intravenous antibiotics can be used. Historically, characteristics of low risk for serious medical complications include outpatient conventional chemotherapy for solid tumors, normal chest x-ray, hemodynamic stability, expected duration of neutropenia ≤ 7 days, normal kidney and liver function tests, early evidence of marrow recovery, malignancy in remission, and normal mental status.

Two classification systems are notable: the Talcott classification¹⁴ of risk groups and a scoring system proposed by the Multinational Association for Supportive Care in Cancer (MASCC)¹⁵ group. Both systems use serious medical complications as the endpoint for risk prediction. However, the sensitivity of the Talcott classification is limited (approximately 30%), and the misclassification rate is high. For example, many patients who do not have complications are not identified by the prediction rule. Also, when the classification system was used on patients discharged for home intravenous antibiotics after 2 days of inpatient observation, the complication rate was higher than anticipated.¹⁶ The MASCC group scoring system is based on patient history, age, outpatient status, clinical status at presentation, and comorbidities.¹⁵ Low-risk patients are identified as those with a score > 20 . This scoring system is suitable for clinicians because of its simplicity and greater sensitivity than the Talcott system. However, the MASCC system has not been studied extensively in outpatients.

Adults at low risk for complications with neutropenic fever may be treated with oral antibiotics.^{17,18} The use of oral antibiotics can be considered for low-risk patients who present only with fever; such patients should have no focus of bacterial infection or symptoms or signs of systemic infection, such as chills or hypotension. Some low-risk

patients can be treated as outpatients; however, many studies that have supported use of oral antibiotics involved hospitalized patients.¹⁸ Close observation and easy access to medical care are essential for patients with febrile neutropenia treated as outpatients. Another outpatient therapy strategy consists of brief inpatient admission with use of intravenous antibiotics, obtaining cultures and results, and excluding serious infection prior to discharge with oral antibiotics.

Initial antibiotic therapy

Early antibiotic therapy is warranted in febrile neutropenic patients because infections can progress rapidly. Bacterial infections may not be easy to distinguish from noninfections in neutropenic patients with fever. Empiric antibiotics should also be considered for afebrile neutropenic patients who have signs and symptoms of infection (Table 2). Considerations influencing antimicrobial selection include center-specific factors (namely local patterns of antibiotic resistance) and patient-specific factors (recent antibiotics, quinolone prophylaxis, drug allergies, and signs and symptoms).

Need for empiric vancomycin

Indications for empiric use of vancomycin for febrile neutropenia include clinically suspected catheter-related infection, known colonization with penicillin- or cephalosporin-resistant organisms or colonization with methicillin-resistant *S. aureus*, blood cultures positive for gram-positive organisms (before identification and susceptibility testing), or hypotension.¹⁹ In some centers, intense chemotherapy with mucosal damage and quinolone prophylaxis are also indications for empiric vancomycin. For patients with an indication for empiric vancomycin, or colonized with vancomycin-resistant organisms, linezolid may be an alternative. A recent randomized clinical trial demonstrated similar efficacy and safety outcomes

with linezolid and vancomycin in a study of febrile neutropenic patients with cancer.²⁰ The potential for myelosuppression secondary to linezolid, however, may be a concern.

Monotherapy or combination therapy

Studies have shown no difference in outcome between monotherapy and combination therapy for empiric treatment of uncomplicated episodes of fever in neutropenic patients.²¹⁻²⁴ All of the drugs recommended for monotherapy have an adequate initial broad spectrum in most settings. A third- or fourth-generation cephalosporin (ceftazidime or cefepime [Maxipime]) or a carbapenem (imipenem-cilastatin [Primaxin] or meropenem [Merrem]) may be used as monotherapy. However, extended-spectrum beta-lactamases and type-1 beta-lactamases have reduced the effectiveness of ceftazidime for monotherapy.²⁵ Also, in contrast to ceftazidime, excellent activity against viridans streptococci and pneumococci is demonstrated by imipenem-cilastatin, meropenem, and cefepime. Piperacillin-tazobactam (Zosyn) has been studied less extensively as monotherapy for febrile neutropenia compared with other antimicrobials.²³

The most common combination regimens (not including vancomycin) include piperacillin-tazobactam or ticarcillin-clavulanic acid (Timentin) with an aminoglycoside (gentamicin, tobramycin, or amikacin [Amikin]), an antipseudomonal cephalosporin (cefepime or ceftazidime) with an aminoglycoside, and a carbapenem (imipenem-cilastatin or meropenem) with an aminoglycoside. The possible advantages of combination therapy include potential synergy against some gram-negative organisms,²⁶ reduced risk of emergence of drug-resistant bacteria,²⁷ and a wider spectrum. Disadvantages of combination therapy include higher cost, increased toxicity, and the need for laboratory monitoring of drug levels for aminoglycosides.

Duration of therapy

Antibiotic therapy for at least 3-5 days is generally required to determine the efficacy of the empiric regimen. Decisions regarding management of the empiric treatment are based on whether a documented infection is present, the infection has resolved, or the patient's condition has worsened. The most important factor in deciding when to stop antimicrobial therapy in febrile neutropenia is the ANC.

Afebrile by days 3-5 of empiric treatment

If an infection is documented, therapy can be adjusted to treat the causative organism, but broad-spectrum antibiotics should be maintained to prevent breakthrough bacteremia. Antibiotic therapy should be given for at least 7 days or until cultures are sterile and the patient is clinically improved. Achieving an ANC ≥ 500 cells/mm³ is favorable but may not be necessary if neutropenia is prolonged and clinical and microbiologic improvements are noted.

If the patient is at low risk and no infectious etiology is identified, an intravenous regimen can be switched to an oral regimen of amoxicillin-clavulanate and ciprofloxacin (Cipro).¹⁸ The same intravenous antibiotics should be continued for high-risk patients. Antibiotics can be stopped once the patient is afebrile and the ANC is ≥ 500 cells/mm³ for 48 hours. If patients at initial low risk who are clinically stable become afebrile by days 3-5 of empiric therapy and the ANC remains < 500 cells/mm³ by day 7, antibiotics can be stopped when they are afebrile for 5-7 days. Patients at initial high risk, with an ANC < 100 cells/mm³, mucositis, or unstable vital signs, should remain on antibiotics through the neutropenic period.

Persistent fever through days 3-5 of treatment

Fever that persists > 3 days in neu-

tropenic patients on empiric antibiotic therapy with no site of infection documented and culture results negative warrants reassessment. Possibilities include a nonpyogenic infection, a drug-resistant organism, slow response to empiric antibiotics, emergence of a secondary infection, a subtherapeutic drug level, or a drug fever. Some patients with documented infections may need ≥ 5 days of therapy for fever to resolve.^{28,29}

Reevaluation includes careful physical examination, review of culture results, repeat cultures, examination of catheter sites, and additional diagnostic imaging of suspected sites of infection. Serum drug levels can be checked if possible, and computed tomography of the sinuses, chest, or abdomen can be performed if indicated. If no source of fever is identified, the same antibiotic regimen can be continued if the patient is stable and clinically unchanged, antibiotics can be added or adjusted if progressive disease or drug toxicity is apparent, or an antifungal agent can be added to the antibiotic regimen if resolution of neutropenia does not appear to be imminent.⁸

If the patient remains febrile on days 3–5 of broad-spectrum antibiotics and no infectious source of fever is found, antibiotics can be stopped

4–5 days after the ANC recovers to > 500 cells/mm³. Reassessment should be directed at fungal, mycobacterial, or viral pathogens. If fever persists and the ANC remains < 500 cells/mm³, antibiotics are continued for 2 weeks and the patient reevaluated; if the patient is clinically stable and no infection is identified, antibiotics can be stopped.⁸ When antibiotics are stopped while patients are neutropenic, they need to be monitored closely and antibiotics restarted if fever or signs of infection develop.

Empiric antifungal therapy

During the first week of febrile neutropenia, evaluations of the cause of fever focus on bacterial pathogens. *Candida* species are the most common fungal pathogens during neutropenia, typically occurring during neutropenic episodes lasting > 1 week, and *Aspergillus* species are less common, usually occurring with prolonged neutropenia lasting > 2 –3 weeks. Fungal infections are generally not a problem during neutropenic episodes lasting < 1 week after chemotherapy.

Past studies have shown that use of empiric antifungal therapy in neutropenic patients with persistent fever reduced mortality compared with patients who did not receive empiric antifungal therapy. Trials performed in the 1980s support the effectiveness of amphotericin B (AmB) in decreasing fungal infections and mortality in persistently febrile neutropenic patients.^{30,31} Until recently, AmB was the drug of choice for febrile neutropenia not responding to broad-spectrum antibiotics. A smaller study comparing itraconazole (Sporanox) and AmB demonstrated higher rates of clinical success (composite of defervescence, absence of breakthrough fungal infections, and absence of adverse drug events) with itraconazole but similar rates of fungal infections.³²

In a clinical trial comparing liposomal AmB (AmBisome) and AmB,

liposomal AmB was as successful, less nephrotoxic, and associated with fewer infusion-related toxicities.³³ Several other randomized trials have evaluated lipid formulations of AmB, including AmB colloidal dispersion,³⁴ lower doses of liposomal AmB,³⁵ and comparisons of liposomal AmB and lipid complex,^{36,37} suggesting that all lipid formulations are comparably effective, with the liposomal version being the least toxic.

Voriconazole (Vfend), a second-generation triazole with an extended spectrum that includes molds, was compared with liposomal AmB.³⁸ The overall success rates were not significantly different, but because of the trial's predetermined confidence interval requirement and definition of noninferiority, voriconazole did not demonstrate noninferiority.

More recently, caspofungin (Candidas), of the echinocandin class, was compared in a randomized trial with liposomal AmB as empiric antifungal therapy.³⁹ Clinical success rates were similar in both groups, with fewer drug-related adverse events in the caspofungin arm. Thus, there are now several antifungal options for empiric antifungal treatment of febrile neutropenia.

Antibiotic prophylaxis for afebrile neutropenic patients

Although empiric antibiotic therapy for febrile neutropenia is standard, antibiotic prophylaxis for afebrile neutropenic patients remains controversial. Past studies have shown that antibiotic prophylaxis decreases febrile episodes and infections during neutropenia, but decreases in mortality are less consistent.⁴⁰ A meta-analysis of 100 randomized clinical trials demonstrated a small reduction in mortality with antibiotic prophylaxis, particularly with fluoroquinolones.⁴¹ Recent studies of fluoroquinolone prophylaxis showed reduced rates of infection and fever,^{42,43} but they were not powered to demonstrate changes

TABLE 2

Empiric antibiotic therapy

Monotherapy

- Antipseudomonal third-generation cephalosporin (ceftazidime)
- Fourth-generation cephalosporin (cefepime)
- Carbapenem (imipenem-cilastatin or meropenem)

Combination therapy

- Piperacillin-tazobactam + aminoglycoside (gentamicin, tobramycin, or amikacin)
- Ticarcillin-clavulanic acid + aminoglycoside
- Antipseudomonal cephalosporin + aminoglycoside
- Carbapenem + aminoglycoside

in mortality. Despite evidence for efficacy of antibiotic prophylaxis in reducing infections, current guidelines do not recommend routine prophylaxis with antibiotics because of concern for emergence of drug-resistant organisms with widespread antibiotic use and lack of consistency demonstrating reductions in mortality rates.⁸

Use of colony-stimulating factors

The use of colony-stimulating factors has been studied in several randomized controlled trials.⁴⁴⁻⁴⁷ Past trials have shown that granulocyte colony-stimulating factor (filgrastim, Neupogen) and granulocyte-macrophage colony-stimulating factor (sargramostim,

Leukine) decrease the duration of neutropenia during episodes of febrile neutropenia but have not decreased infection-related mortality. However, other measures of morbidity of febrile neutropenia, such as the duration of fever, the use of antimicrobials, and costs, are not decreased with the use of hematopoietic growth factors.

Therefore, current guidelines on oncologic and infectious diseases recommend against the routine use of colony-stimulating factors for uncomplicated cases of fever and neutropenia.^{8,48} In certain cases, the use of colony-stimulating factors may be indicated, such as with prolonged marrow recovery, severe infections or sepsis, or documented infections not responding to antimicrobial therapy

in patients who remain neutropenic.

Conclusion

Management of patients with febrile neutropenic fever is complex and involves careful consideration of multiple factors. At least one-half of neutropenic patients who become febrile have a documented or occult infection. The microbiology of infections has shifted, with more gram-positive infections, increased drug resistance, and previously less common organisms being seen more frequently. Risk assessment is needed to determine whether inpatient or outpatient treatment is indicated and whether intravenous or oral antibiotics can be used.

Empiric monotherapy with a third- or fourth-generation cephalo-

Case studies: management strategies in action

Case 1:

A 59-year-old woman is diagnosed with early-stage breast cancer. Her primary tumor is a 3.5-cm, estrogen receptor-positive, HER-2/neu negative infiltrating ductal carcinoma with a positive sentinel lymph node. Her absolute neutrophil count (ANC) is 400 cells/mm³. Adjuvant chemotherapy with TAC (Taxol [paclitaxel], Adriamycin [doxorubicin], cyclophosphamide) is administered every 3 weeks. After 9 days of treatment, she has a temperature of 102°F. What management strategy is indicated in this patient?

The main decisions in this case involve whether the patient can be treated as an outpatient or an inpatient and whether intravenous or oral antibiotics need to be used. Careful risk assessment can provide the answers. Historically, characteristics of patients at low risk for serious medical complications include conventional outpatient chemotherapy for solid tumors, hemodynamic stability, a normal chest x-ray, expected duration of neutropenia \leq 1 week, normal liver and kidney function

tests, early evidence of marrow recovery, malignancy in remission, and normal mental status. Although not studied extensively in outpatients, a scoring system, such as the MASCC group scoring system, which is based on patient history, age, outpatient status, comorbidities, and clinical status at presentation, can also be used. Low-risk patients can be identified with a score $>$ 20. If this patient is considered at low risk for medical complications by these criteria, an outpatient oral antibiotic regimen of ciprofloxacin and amoxicillin-clavulanate may be an option if close monitoring and prompt access to medical care can be ensured.

Case 2:

A 66-year-old man is diagnosed with intermediate-grade diffuse large cell non-Hodgkin's lymphoma. A course of CHOP-rituximab (Rituxan) chemotherapy is planned on a 3-week cycle. Would you give him a white blood cell (WBC) growth factor during the first cycle, or wait to see whether he has an episode of febrile neutropenia and then

give him a WBC growth factor with all subsequent cycles?

Although routine use of WBC growth factors is not recommended for uncomplicated cases of febrile neutropenia, risk assessment can help to determine whether a patient is at risk for complications of chemotherapy, including neutropenia and febrile neutropenia. Risk models have identified advanced age, poor performance status, comorbidities, low baseline blood cell counts, and high chemotherapy dose intensity as predictors of neutropenic complications. Most cases of febrile neutropenia occur during the first cycle of chemotherapy. When the anticipated risk of febrile neutropenia is as low as 20%, both the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) guidelines suggest using prophylactic WBC growth factors.^{48,49} If the patient in this case meets these criteria, targeted use of prophylactic colony-stimulating factors may be considered.

sporin or a carbapenem is as effective as combination therapy, and vancomycin can be used when certain criteria are met. Fungal infections should be considered during episodes of prolonged febrile neutropenia despite broad-spectrum antibiotics. Many newer antifungal agents are now available, which are effective and less toxic than AmB. Antibiotic prophylaxis for afebrile neutropenic patients and use of colony-stimulating factors during episodes of febrile neutropenia are not recommended routinely because of lack of data demonstrating consistent reduction in mortality. Shifts in the types of organisms and increased drug resistance pose new challenges, and further research and drug development are needed to ensure adequate treatments.

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