Chapter 36
Current Treatment of Febrile Neutropenia: Tailored, Individual Based Therapy

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36.1 Introduction

Cancer patients can have significant myelosuppression secondary to chemotherapy that they receive as part of their treatments. Susceptibility to infection during this time is high as a result of disruption in the mucosal barrier in the gastrointestinal tract, in addition to translocation from other sites as well as indwelling foreign devices that may be colonized. Since the ability to mount an inflammatory response is diminished during myelosuppression, fever may be the only sign of a brewing infection.

Since, morbidity and mortality as a result of infectious complications is high in the setting of neutropenia, it is imperative that empiric antimicrobial treatment is promptly instituted when fever develops. Prior to the era of empiric antibiotic therapy, infections accounted for most episodes of neutropenic fever and approximately 70 % of the mortality in neutropenic acute leukemia patients [1]. Benefit of using empiric antibiotic therapy rather than waiting for microbiology results was recognized in the 1960s and early 1970s and has been a standard practice since. Up till the 1990s inpatient treatment with intravenous antibiotics was preferred, however, now based on risk stratification, outpatient treatments may be undertaken in a selected group of patients. Choice of antimicrobials is based primarily on degree

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and duration of neutropenia with broad-spectrum agents used for patients with severe, profound and prolonged neutropenia who have a higher risk of adverse outcomes [2].

36.2 Definition

A sustained temperature of greater than 38° centigrade for greater than 1 h or one time reading of 38.3° centigrade is generally agreed upon as a definition of fever of neutropenia if the absolute count is less than 500 cells per microliters or is expected to drop below this level in the next 48 h.

Since, temperature measurement plays a crucial role in initiation of treatment protocols in the setting of neutropenia, it is important that a reliable method is used for this. No method is universally agreed upon and practices vary by institutions. Infectious Diseases Society of America (IDSA) discourages the use axillary temperature measurement because of its lack of reliability [2]. Rectal temperature measurement is avoided to prevent introduction of gastrointestinal flora into the blood stream through a disrupted mucosal barrier. Similarly oral temperature should not be measured in the setting of mucositis. Therefore, most institutions prefer non-invasive methods like infrared tympanic temperature measurement. However, falsely high readings may be measured in the dependent ear and cerumen impaction can lead to falsely low readings.

Specific definitions of neutropenia vary slightly between guidelines issued by different bodies. For example, American Society of Clinical Oncology (ASCO) defines an absolute neutrophil count of less than 1,000 cells per microliters as neutropenia, and refers to it as profound and severe if counts are below 500 and 100 cells per microliters respectively [3]. IDSA on the other hand uses a cutoff of less than 500 cells per microliters as a definition of neutropenia. Both, ASCO and IDSA endorse a body temperature of greater than equal to 38.3° centigrade as fever in the setting of neutropenia [2].

36.3 Source of Infectious Organisms

Historically, gram-negative bacteria like Pseudomonas have been the cause of severe infections, mostly trans-locating across the breached mucosa of the gastrointestinal tract [4]. However, lately, there has been a shift towards more gram-positive organisms [5]. Increased and prolonged use of indwelling infusion catheters has been often sited as a reason. Fungal and viral infections are more common in patients with prolonged neutropenia and a history of multiple chemotherapeutic uses.

Currently, coagulase negative Staphylococci are the most frequently identified organisms from blood cultures but the incidence of multi drug resistant gram-

Table 36.1 Common bacterial pathogens in febrile neutropenia patients

Common gram-positive pathogens			Common gram-negative pathogens		
Organisms	Resistance mechanism	Mode of entry	*Organisms*	Resistance mechanism	Mode of entry
Coagulase-negative Staphylococci		CVC	*Escherichia coli*	Extended spectrum beta-lactamase	Bowel mucosa
Staphylococcus Aureus	Methicillin-resistant	Skin, CVC	*Klebsiella species*	Carbapenemase-producing	Bowel mucosa
Enterococcus species	Vancomycin resistance	Urine, CVC			

CVC= Central Venous Catheter

negative organisms is on the rise as well. That said, often, the causative organism is not identifiable from cultures in a patient with febrile neutropenia. Anaerobic and polymicrobial infections appear to be a less common source of infection in febrile neutropenia patients (Table 36.1).

Shift from gram-negative organisms and rise in incidence of gram-positive bacteremia is in part due to use of prophylactic antibiotics that predominantly have a gram-negative coverage and increased use of chronic indwelling venous catheters respectively. However, more severe infections are still caused by gram-negative organisms.

Fungal infections are a less common cause of initial fever in the setting of neutropenia [5]. However, the risk of fungal infection increases with the duration and severity of neutropenia, prolonged use of antibiotics and number of chemotherapy cycles given. Candida spp. and Aspergillus spp. are the most common causes of disseminated fungal infection. Candida often colonizes the gut and is translocated across a breached mucosa in neutropenic patients, where as the mode of transmission of Aspergillus is inhalation. Candida Albicans account for most cases of candida infections, however, incidence of non Albican Candida species is on the rise given frequent use of fluconazole in this patient population. Life threatening 'rhino-orbital-cerebral' infections by Mucor-mycosis is not uncommon in immunocompromised patients and therefore health care providers should have a low threshold for suspicion for this. In patients who live in or travel to endemic areas, reactivation of endemic fungi (Histoplasma Capsulatum, Blastomyces dermatitidis, and Coccidioides spp.) should also be considered.

Viral infections, especially secondary to reactivation of human herpes viruses, are common in high-risk neutropenic patients. Most HSV 1 and HSV 2 infections occur because of reactivation in immunocompromised host and can cause of wide array of clinical manifestations, ranging from ulceration of oral/genital mucosa to meningitis, encephalitis and myelitis [6]. Varicella Zoster Virus tends to cause disseminated infection as well in immunocompromised host. Primary infection and reactivation of CMV, EBV and HHV 6 are also seen in patients who have undergone hematopoietic stem cell transplant and can cause of wide range of problems including significant bone marrow suppression.

36.4 Initial Assessment and Workup

A thorough history and physical examination is very important when assessing a neutropenic patient for fever. Especial attention should be paid to signs or symptoms that may help determine the source of infection. Information about duration and severity of neutropenia and other co-morbid medical conditions may help select patients who may be suitable for outpatient treatment. Patients in extremis, presenting with signs of hypotension and respiratory distress would require a more intensive form of care. A low threshold of suspicion is crucial to identify neutropenic patients who may not present with fever but go on to develop septicemia. These individual may only have significant fatigue as a presenting symptom. Steroids tend to mask fevers and this should be taken into consideration when evaluating a patient with neutropenia [7].

Laboratory tests should include a CBC count with differential leukocyte count and platelet count; measurement of serum levels of creatinine and blood urea nitrogen; and measurement of electrolytes, hepatic transaminase enzymes, and total bilirubin. At least two sets of blood cultures are recommended, with a set collected simultaneously from each lumen of an existing central access, if present, and from a peripheral vein site; two blood culture sets from separate venipunctures should be sent if no central catheter is present. Chest X ray should be ordered for patients with respiratory symptoms per IDSA guidelines. Routine use of CT scans is not advocated by IDSA but most oncologists prefer to use that for evaluation of pulmonary symptoms. A broad-spectrum antibiotic, with or without multiple drug resistant gram-positive coverage (determined by degree suspicion of central line infection or presence of hemodynamic compromise) should be instituted within an hour of presentation per ASCO recommendations.

Assessment of risk for complications of severe infection should be undertaken at presentation of fever. Risk assessment may determine the type of empirical antibiotic therapy (oral vs IV), venue of treatment (inpatient vs outpatient), and duration of antibiotic therapy. Most experts consider high-risk patients to be those with anticipated prolonged (>7 days duration) and profound neutropenia (ANC <100 cells/mm^3 following cytotoxic chemotherapy) and/or significant medical co-morbid conditions, including hypotension, pneumonia, new-onset abdominal pain, or neurologic changes. Such patients should be initially admitted to the hospital for empirical therapy. Low-risk patients, including those with anticipated brief (<7 days duration) neutropenic periods or no or few comorbidities, are candidates for oral empirical therapy. Formal risk classification may be performed using the MASCC scoring system [8]. Patients with a MASCC score of less than 21 are considered high risk and per IDSA guidelines, all patients at high risk by MASCC or by clinical criteria should be initially admitted to the hospital for empirical antibiotic therapy. Low-risk patients have a MASCC score >21. Carefully selected low-risk patients may be candidates for oral and/or outpatient empirical antibiotic therapy [9]. It is important to note that a subset of patient deemed low risk by MASCC may go on to develop serious complications. Among these are patients with a major abnormality (or

Table 36.2 The multinational association for supportive care in cancer risk-index score

	Characteristic weight
Burden of febrile neutropenia with no or mild symptoms	5
No hypotension (systolic blood pressure 0.90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematologic malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms	3
Outpatient status	3
Age, 60 years	2

significant clinical worsening since the most recent chemotherapy or onset of neutropenia) with respect to any of the following: organ dysfunction, comorbid conditions, vital signs, clinical signs or symptoms, documented anatomic site of infection (Table 36.2).

36.5 Choice of Anti-microbials

36.5.1 Antibiotics

High-risk patients require hospitalization for empiric, intra venous antibiotics. Monotherapy with a broad spectrum, anti-Pseudomonal, beta lactam drug like cefepime, a carabapenem (meropenem or imipenem-cilastatin), or piperacillin-tazobactam is recommended as the initial therapy. Vancomycin is not recommended as initial therapy by IDSA, but should be considered in specific clinical scenarios in addition to monotherapy; including suspected catheter-related infection, skin or soft-tissue infection, pneumonia, or hemodynamic instability. Antibiotic regimens may be altered based on culture results or if infection with a multi drug resistant organism is suspected. These include methicillin-resistant Staphylococcus Aureus (MRSA), vancomycin-resistant enterococcus (VRE), extended-spectrum b-lactamase (ESBL) – producing gram-negative bacteria, and carbapenemase-producing organisms, including Klebsiella Pneumoniae carbapenemase (KPC). Risk factors include previous infection or colonization with the organism and treatment in a hospital during specific endemic infection.

An IV-to-oral switch in antibiotic regimen may be made if patients are clinically stable and gastrointestinal absorption is not compromised. Selected hospitalized patients who meet criteria for being at low risk may be transitioned to the outpatient setting to receive either IV or oral antibiotics, as long as adequate daily follow-up is ensured. If fever persists or recurs within 48 h in outpatients, hospital re-admission is recommended, with management as for high-risk patients. Empirical antifungal coverage should be considered in high-risk patients who have persistent fever after 4–7 days of a broad-spectrum antibacterial regimen and no identified fever source.

Per IDSA guidelines, patients with documented Type I hypersensitivity to penicillins may be given ciprofloxacin plus clindamycin or aztreonam plus vancomycin as an alternative. Some low risk patients may be considered for outpatient treatment with oral antibiotics. A combination of ciprofloxacin plus amoxicillin-clavulanate is recommended as initial empiric therapy. However, quinolones should not be used for empiric therapy in patients taking it for prophylaxis.

Duration of antibiotic treatment is determined by the site and source of infection. If no evidence of source of infection is found, treatment should at least be continued till the time of absolute neutrophil count recovery to greater than >500 cells/mm^3, provided patient has remained afebrile.

36.5.2 Antifungal Agents

Empiric antifungal treatment should be considered in patients with persistent or recurrent fever after 4–7 days of antibiotics and whose overall duration of neutropenia is expected to be greater than 7 days. Choice of agent and duration of therapy is based on the suspected or isolated fungal agent. Candida spp. causes invasive infections most commonly in neutropenic patients, however, patients receiving prophylactic fluconazole, are likely to be infected with fluconazole resistant species like Candida Glabrata and Candida Krusei.

The 2010 IDSA guidelines for empiric antifungal therapy recommend amphotericin B deoxycholate, a lipid formulation of amphotericin B, caspofungin, voriconazole, or itraconazole as suitable options for empiric antifungal therapy in neutropenic patients. However, the choice of agent should be based on the suspected infection. For example, caspofungin and drugs from the echinocandin family should not be used when an invasive Aspergillus infection is suspected and lipid formulation of amphotericin b or voriconazole should be preferred instead. Caspofungin, however, is a reasonable choice for suspected candida infections. For persistently febrile patients who have been receiving anti-mold prophylaxis, a different class of antifungal agent with activity against molds should be used for empiric therapy. For example, if voriconazole or posaconazole has been used for prophylaxis, an amphotericin B formulation should be used. Low risk patients usually do not require empiric treatment with antifungal agents, as the risk of fungal infection is low in this patient population.

36.5.3 Antiviral Agents

Antiviral treatment for HSV or varicella-zoster virus (VZV) infection is only indicated if there is clinical or laboratory evidence of active viral disease. However, herpes simplex virus (HSV) – seropositive patients undergoing allogeneic HSCT or leukemia induction therapy should receive acyclovir antiviral prophylaxis. Influenza

virus infection should be treated with neuraminidase inhibitors if the infecting strain is susceptible. In the setting of an influenza exposure or outbreak, neutropenic patients presenting with influenza-like illness should receive treatment empirically.

36.5.4 Granulocyte Colony Stimulating Factor (CSF)

Use of myeloid CSFs are not recommended as adjuncts to antibiotics for treating established fever and neutropenia. Although days of neutropenia, duration of fever, and length of hospital stay have been minimally (but statistically significantly) decreased in some randomized studies, the actual clinical benefit of these reductions is not convincing and therefore not strongly advocated for by most experts.

36.6 Conclusion

Febrile neutropenia is a serious medical condition that is prevalent among cancer patients. Thanks to improved microbiological laboratory techniques and integration of growth factor usage into the chemotherapy regimens, the mortality directly caused by this condition has been decreasing. However, a dynamic shift of causative organisms secondary to indwelling catheter use, resistance to the antibiotics still remain as a challenge for oncologists and patients. Thus, careful risk stratification of patients, proper initial evaluation of patient's condition and treatment history, as well as continued development of preventive measure are warranted.

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