Chapter 45
Current Treatment of Febrile Neutropenia

Focused on the Individual Who Undergoes Treatment for Breast Cancer

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Abstract Chemotherapy-induced neutropenia (CIN) is a common side effect of anticancer drugs used for treatment of solid tumors. Neutropenic cancer patients are more than 50 times more likely to develop an infection, often bacterial, which can develop febrile neutropenia (FN), a toxicity that requires rigorous treatment. FN is not only potentially life-threatening, but may also alter the patient's chemotherapy schedule to impact their long-term outcomes. The significant impact of CIN and FN on cancer patients makes it imperative to develop a standardized guideline of prophylactic treatment of CIN. Thus, we conducted a literature review to provide a guideline that compiles guidelines from reputable cancer treatment institutions. Currently, guidelines differ slightly between sources and yet agree upon the vast majority of core practice to ensure the patient safety which we present here to provide as a practice guideline.

Keywords Neutropenic fever · Febrile neutropenia · Post-chemotherapy neutropenia

45.1 Introduction

Breast cancer accounts for a large amount of diagnoses, with an estimated 266,120 new cases diagnosed in women in the United States every year, and more so world wide [1]. Conversely, the mortality rate has gone down in the past years with the advent of stronger, more targeted anticancer drugs [2]. However, a common side

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effect associated with anticancer treatment is chemotherapy-induced neutropenia (CIN), with 37% of BC patients experiencing a decrease in the absolute neutrophil count (ANC) below 500 cells/mm^3 [3]. Cancer patients can be in danger of transient immunosuppressive status secondary to chemotherapy, and exposed to morbidity and mortality [4]. Cancer patients can have significant myelosuppression secondary to chemotherapy treatment, which increases susceptibility to infection 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. Fever may often be the only sign of infection due to diminished ability to mount an inflammatory response. Since morbidity and mortality caused by neutropenic infection complications are so high [5], it is imperative that empirical antimicrobial treatment is promptly instituted when fever develops. Choice of antimicrobials is based primarily on degree 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. While therapeutics to treat breast cancers may not induce as much as neutropenic fever as other diseases, e.g., hematologic malignancy or stem cell transplantation, still patients suffer from this complications [6]. Physicians must be aware of these guidelines, as well as infection risks, diagnostic methods, and antimicrobial therapies required for managing febrile patients through the neutropenic period. Thus, here we review current updated data and guidelines for neutropenic fever, focusing on patients who undergo breast cancer targeted treatments.

45.2 Definition of Neutropenic Fever/Febrile Neutropenia

Neutropenia is defined by the Common Terminology Criteria for Adverse Events (CTCAE) as "a finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen" [3]. The CTCAE has categorized neutropenia into four grades of severity based on the absolute neutrophil count (ANC):

- Grade 1: ANC from the lower normal limit to 1500 cells/mm^3
- Grade 2: ANC from 1500 to 1000 cells/mm^3
- Grade 3: ANC from 1000 to 500 cells/mm^3
- Grade 4: ANC <500 cells/mm^3

There are no universally agreed upon cut-off values for either temperature or ANC count for definition of FN internationally. For instance, the American Society of Clinical Oncology (ASCO) defines an absolute neutrophil count of less than 1000 cells per microliters as neutropenia, and refers to it as profound and severe if counts are below 500 and 100 cells per microliters respectively. Infectious Disease Society of America (IDSA) on the other hand uses a cutoff of less than 500 cells per microliters as a definition of neutropenia.

The longer the duration of neutropenia, the more likely patients are to develop febrile neutropenia. Febrile neutropenia (FN) is defined by the European Society for Medical Oncology (ESMO) as a temperature of greater than 38.5 °C or two consecu-

tive readings of greater than 38 °C for 2 h while the ANC is below 500 cells/mm^3 [7]. Patients with an ANC of less than 500 cells/mm^3 for greater than 7 days are likely to develop FN, thus needs to take caution/preventive measures not to be exposed to possible infectious source. To define the febrile status here, ASCO endorses a body temperature of greater than equal to 38.3 °C as fever in the setting of neutropenia. IDSA uses a higher cutoff of 38.5 °C but considers a temperature of 38.0 °C that persists for 2 h or more as fever as well [8].

Taking these guidelines for evaluation of neutropenic breast cancer patients into account, a sustained temperature of greater than 38 °C for over 1 h or one time reading of 38.3 °C 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, in which temperatures are measured using non-invasive methods such as infrared tympanic temperature measurements.

45.3 Risk Factors of Developing Neutropenia

A prompt assessment of possible source of infection should be undertaken at presentation of fever for patients who are at risk of FN. However, it is helpful if health care professional is aware of the degree of risk. Few clinical characteristics also contribute to the different risk of FN. Old age, poor performance status (PS), impaired nutritional status, female gender all are considered as risk factors. Previous history of myelotoxicity, extent of disease, hematologic malignancies are also considered as high-risk factors. Among breast cancer patients, the patients who are exposed to dose-dense anthracycline/taxan and docetaxel-based regimens are main ones who are at risk of developing FN but any patients who are exposed to myelosuppressive drugs carry >20% risk of developing neutropenia. In the analysis of Chinese patients who undergo anthracycline based chemotherapy for breast cancer treatment, the occurrence rate was higher among patients with low body mass index (BMI) (<23 kg/m^2), with odds ratio (OR 4.4, 95% CI = 1.65–12.01, p = 0.003) [6].

45.4 Source of Infectious Organisms

Historically, gram-negative bacteria like Pseudomonas have been the cause of severe infection, mostly trans-locating across the breached mucosa of the gastrointestinal tract. However, lately, there has been a shift towards more gram-positive organisms. Increased and prolonged use of indwelling infusion catheters has been often be the source of infection. 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-negative organisms is on the rise as well. That said, often, the causative organism is

Table 45.1 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

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 45.1).

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. However, the risk of fungal infection increases with the duration and severity of neutropenia, prolonged use of antibiotics and number of chemotherapy cycles given [9]. 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, whereas 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 Mucormycosis 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. 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.

45.5 Prevention of Febrile Neutropenia

Prophylactic antibiotics such as myeloid growth factors exhibit some efficacy at reducing the risk of febrile episodes in neutropenic patients with BC. There is evidence that they reduce the risk of FN and infection in patients. Granulocyte colony-stimulating factor has demonstrated, through randomized controlled trials, a significant reduction in infection-related and early all-cause mortality as it improves delivery of chemotherapy dose intensity. For patients receiving chemotherapy associated with a 20% or greater risk of FN, current guidelines recommend primary prophylaxis with myeloid growth factor. Truong et al. analyzed total of 130 studies with various regimen to treat cancer including >50,000 patients. In this study, randomized study represented more accurate rate of FN, which was 13% [10].

Given the importance, reputable cancer organization publishes the guidelines for the use of growth factor, including short and long acting agents. In breast cancer, a multi-center, double-blinded, randomized phase III study was conducted using pegfilgrastim in patients who undergo treatment for breast cancer. This study published by Vogel et al., showed that a significant lower risk of FN (1% vs 17%, in prophylactic filgrastim using arm vs not, respectively), as well as FN related hospitalization (1% vs 14%), use of IV antibiotics (2% vs 10%), supporting the role of prophylactic use of neutrophil support as part of standard care for patients with breast cancer [11]. Indeed, some regimens in breast cancer treatment, e.g., dose dense AC or taxol, the use of supportive filtrastim or pegfilgrastim is mandatory.

45.6 Management of Neutropenic Fever

45.6.1 History Taking and Physical Exam: Risk, Source Assessment

Patient history and physical examination should be a primary factor when assessing a neutropenic patient for fever, with special attention paid to signs and symptoms that can help determine any sources of infection. Information about duration and severity of neutropenia and other co-morbidities can be used to identify patients as high-risk or low-risk, which affects the rigor of empirical treatment. Risk assessment can help determine the type of empirical antibiotic therapy (IV vs. oral), venue of treatment (inpatient vs. outpatient), and duration of antibiotic therapy. MASCC and CISNE risk stratification can be utilized [12].

High-risk patients exhibit or are anticipated to have prolonged (greater than 7 days) and profound neutropenia (ANC less than 100 cells/mm^3 following cytotoxic chemotherapy) with significant co-morbidities such as hypotension, pneumonia, new-onset abdominal paint, and neurological changes [4]. They may present in extremis, with signs of hypotension and respiratory distress. These individuals may only have significant fatigue as a presenting symptom. Steroids also tend to mask

fevers and should be taken into consideration when evaluating a patient with neutropenia.

Low-risk patients exhibit a brief duration (less than or equal to 7 days) of neutropenia with few to no co-morbidities. They are good candidates for oral empirical therapy and can be treated with outpatient empirical antibiotic therapy [4]. Formal risk classification can be performed using the Multinational Association for Supportive Care in Cancer (MASCC) scoring system as an example. Many institutions carry their own guideline of assessing risk for patients who came in for the urgent care [13] (Table 45.2).

Patients with high scores are at higher risk while those who score higher are at lower risk. High-risk patients are defined by IDSA guidelines as having a MASCC score of less than 21. Low-risk patients are defined by IDSA guidelines as having a MASCC score of greater than or equal to 21 [4]. It is important to note that a subset of patients deemed low-risk by the MASCC scoring system may go on to develop serious complications. Among these are patients with a major abnormality or 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, and/or documented anatomic site of infection.

45.6.1.1 Laboratory Workup

After clinical evaluation, laboratory tests should be performed. Tests should include a complete blood cell (CBC) count with differential leukocyte count and platelet count; chemistry panel. At least two sets of blood cultures are recommended, with each set collected simultaneously from each lumen of an existing central venous catheter (CVC), or from two separate venipunctures if no central catheter is present. Culture specimens from other sites of suspected infection should be obtained as clinically indicated, and a chest radiograph should be ordered for patients with respiratory symptoms.

Table 45.2 The multinational association for supportive care in cancer risk-index score (MASCC)

Characteristic	Characteristic Weight
Burden of febrile neutropenia with no or mild symptoms	5
No hypotension (systolic blood pressure ≥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

MASCC risk-index score [13]

45.6.1.2 Antibacterial Antibiotics

High risk patients require hospitalizations for empirical broad spectrum intravenous antibiotic therapy, and necessary supportive care depends on the degree of severity. A low threshold of suspicion is crucial to identifying neutropenic patients who may not present with fever but go on to develop septicemia. Duration of antibiotic treatment is determined by the underlying condition, suspected route 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. A broad -spectrum antibiotic, with or without multiple drug resistant gram-positive coverage (determined by degree of suspicion of the central line infection or presence of hemodynamic compromise), should be instituted within an hour of presentation per ASCO recommendations [14].

Gram-positive organisms have been a predominant bacterial pathogen for febrile neutropenia. Monotherapy with a broad spectrum, anti-pseudomonal, beta lactam drug is recommended as the initial therapy. Drugs that fall under this category include cefepime, a carabapenem (meropenem or imipenem-cilastatin), or piperacillin-tazobactam. Approximately 10%–15% of bacteremias are polymicrobial, which encourages the use of combination regimens. 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 that carried regional endemics [15]. Cochrane Review recently published an updated guidelines of the choice of antibiotics in patients with FN, with gram-positive bacteria.

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 prophylaxsis.

For rigorous management of patients who are at risk of this significantly high risk condition, a dedicated team of health care providers familiar with risk-based therapy should monitor and follow-up with outpatient low-risk patients. A management team (e.g., emergency departments, pharmacy, support services) should be accessible 24 h a day. The hospital should also provide transportation for the patient within proximity to the cancer treatment center.

45.6.1.3 Antifungal Agents

Invasive fungal infections are most often seen in patients with prolonged neutropenia and after stem-cell transplantation. 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 species 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. Oral candidiasis is the most commonly noted fungal infection in patients with breast cancer, and the treatment can also be introduced orally either by oral fluconazole, nystatin [16].

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 other 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 do not require empiric treatment with an antifungal agent as the risk of fungal infection is low in this patient population. Majority of patients who undergo breast cancer treatment do not carry high risk for fungal infection, however given recent surge of new immunotherapy and targeted therapy that may carry different level of risk, providers also should be aware of these possible risks.

45.6.1.4 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.

45.7 Targeted Therapeutics in Breast Cancer and Neutropenia

Recent advancement of the novel targeted therapeutics in breast cancer, also changed the way we think about neutropenia, FN in patients with breast cancer. Two examples of such agents are CDK 4/6 inhibitors and PARP inhibitors. CDK4/6 inhibitors have been approved as a standard care therapy option for patients with hormone receptor positive breast cancers, either as single agent or combination. Among three FDA approved CDK 4/6 inhibitors, palbociclib and ribociclib showed around 4–7% rate of FN [17–19]. Abemaciclib, which is more specific inhibitor of CDK4, had lower rate of neutropenia and lower rate of febrile neutropenia (1/132), and yet still around 46% patients still experienced various grade of neutropenia [20, 21]. Actual hospitalization and other seqale related to severe mortality caused by neutropenia from CDK4/6 inhibitors are not as frequent as chemotherapeutics.

Poly ADP ribose polymerase (PARP) inhibitor, is another category of novel targeted therapy that can cause cytopenia, including neutropenia. Given dependency of PARP protein in BRCA defective cancer for the repair of cancer cells when nonhomologous end-joining (NHEJ) DNA repair occurs, PARP inhibitors were studied, and shown efficacy in patients wiht germline BRCA mutated cancers, including breast cancer [22]. Olaparib was recently approved for its use by FDA [23], and several other PARP inhibitors, such as veliparib, rucaparib, niraparib, and talazoparib are currently under study in breast cancer. The rate of neutropenia of PARP inhibitors, also ranges around 45–50% [24, 25]. It is important for clinicians pay attention to the neutropenia that can be caused by new category of agents that can cause cytopenias. The principle of managing neutropenia caused by these agents is the same, however the detailed guideline of dose management is well established per each agent.

45.8 Conclusion

Chemotherapy continues to be a mixed blessing because of its association with myelosuppression and its complications, including chemotherapy-induced neutropenia and febrile neutropenia, a serious medical condition that is prevalent among cancer patients. Management of these side effects is imperative to the health of the patient, and requires clinical and laboratory evaluation, risk assessment, and treatment with empiric broad-spectrum antibiotics. 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, new targeted therapy that can cause bone marrow suppression still remain as a challenge for oncologists and patients. Thus, careful risk stratification of patients, proper initial evaluation of condition and treatment history of individual patients, as well as continued development of preventive measure are warranted.

Multiple Choice Questions

1. What are key features of neutropenic fever?

   I. Body temperature of greater than 38.5 degrees centigrade
   II. Three consecutive body temperature readings of greater than 38 degrees centigrade for 2 h
   III. Decreased number of neutrophils in blood

   (a) I and II
   (b) I and III
   (c) II and III
   (d) I, II, and III

Correct answer: B
Comments: For answer II, only two consecutive body temperature readings are necessary.

2. Which of the following accurately describes one grade of severity of febrile neutropenia based on CTCAE guidelines?

   (a) Grade 1: ANC from the lower normal limit to 1000 cells/mm^3
   (b) Grade 2: ANC from 1200 to 750 cells/mm^3
   (c) Grade 3: ANC from 1000 to 500 cells/mm^3
   (d) Grade 4: ANC < 550 cells/mm^3

Correct Answer: C
Comments: Severity is graded as below:

Grade 1: ANC from the lower normal limit to 1500 cells/mm^3
Grade 2: ANC from 1500 to 1000 cells/mm^3
Grade 3: ANC from 1000 to 500 cells/mm^3
Grade 4: ANC < 500 cells/mm^3

3. What is the suggested guidelines for diagnosing neutropenic fever in breast cancer patients?

   (a) Sustained temperature (>1 h) of greater than 38 degrees centigrade, ANC < 500 cells/μL
   (b) Sustained temperature (>1 h) of greater than 38 degrees centigrade, ANC < 1000 cells/μL
   (c) One time reading of 38 degrees centigrade, ANC < 500 cells/μL
   (d) One time reading of 38 degrees centigrade, ANC < 1000 cells/μL

Correct Answer: A
Comments: The suggested guidelines are as follows: sustained temperature (>1 h) of greater than 38 degrees centigrade or a one time reading of greater than 38.3 degrees centigrade, ANC < 500 cells/μL. If the ANC < 1000 cells/μL and anticipated to have further drop below 500

4. Common risk factors for developing febrile neutropenia include all of the following except:

   (a) Impaired nutritional status
   (b) Exposure to dose-dense docetaxel-based regimens
   (c) Male gender
   (d) Poor performance status (PS)

Correct Answer: C
Comments: Females are more at risk for febrile neutropenia than males.

5. What are the primary components of risk assessment for febrile neutropenia? Select all that apply.

   (a) Patient history
   (b) The patient's age, body temperature, and nutritional status
   (c) Physical examination
   (d) Signs and symptoms that determine source of infection

Correct Answer: A, C, and D
Comments: Answer B is important for evaluating a patient for neutropenic fever, but is not considered primary factors of risk assessment.

6. What is the importance of performing risk assessment on patients with neutropenic fever?

   (a) It can be used to prioritize high-risk patients above low-risk patients when administering treatment
   (b) It must be performed before diagnosing a patient with febrile neutropenia
   (c) It can discover co-morbidities that need to be treated before the neutropenic fever
   (d) It can help determine the type, venue, and duration of antibiotic therapy

Correct Answer: D

Comments: Proper risk assessment can identify patients as high or low risk, which affects the rigor (type, venue, and duration) of empirical treatment. Comorbidities are also considered when determining treatment, but are not priorities for treatment.

7. What characteristics affect a patient's level of risk, as scored by MASCC? Select all that apply:

   (a) Dehydration
   (b) Burden and symptoms of febrile neutropenia
   (c) Age, 55 years
   (d) Hypertension
   (e) Fungal infection
   (f) Pulmonary disease

Correct Answer: A, B, E, F

Comments: For C, the relevant age is 60 years old. For D, hypotension (cystolic blood pressure of 90 mmHg) is important.

8. True or False: The higher the MASCC score, the greater the risk.

Correct Answer: False

Comments: The lower the MASCC score, the greater the risk.

9. Which of the following regarding laboratory tests is false?

   (a) Complete blood cell (CBC) count with differential leukocyte count and platelet count should be performed
   (b) Chemistry panel should be performed
   (c) At least two blood cultures are recommended, to be collected consecutively
   (d) A chest radiograph should be ordered for patients with respiratory symptoms

Correct Answer: C

Comments: At least two sets of blood cultures are recommended, with each set collected simultaneously from each lumen of an existing central venous catheter (CVC), or from two separate venipunctures if no central catheter is present.

10. What are the guidelines for treating high risk patients with febrile neutropenia? Select all that apply.

    (a) Hospitalization for empirical broad spectrum intravenous antibiotic therapy
    (b) Steroid treatment to reduce fever symptoms
    (c) Low threshold of suspicion for patients who do not present with fever but develop septicemia
    (d) If no source of infection is found, treatment should be continued until recovery of ANC to >500 cells/mm^3

Correct Answer: A, C, and D

Comments: Answer B is not a treatment of febrile neutropenia. However, steroids may make diagnosis of febrile neutropenia in neutropenia patients more difficult since it masks fever symptoms.

11. Which of the following drugs is not categorized as a monotherapy with a broad spectrum, anti-pseudomonal, beta lactam drug?

    (a) Cefepime
    (b) Carabapenem
    (c) Piperacillin-tazobactam
    (d) Ciprofloxacin

Correct Answer: D

Comments: Ciprofloxacin is an orally ingested antibiotic that is used as an alternative to penicillin on clinically stable patients with Type I hypersensitivity to penicillins.

12. What is the most common cause of infection among patients with febrile neutropenia?

    (a) Gram-positive bacteria
    (b) Gram-negative bacteria
    (c) Fungi
    (d) Virus

Correct Answer: B

Comments: Gram-negative bacteria, specifically coagulase negative Staphylococci, are the most frequently identified organisms from blood cultures. However, the incidence of multi drug resistant gram-negative organisms as well as gram-positive bacteria are on the rise.

13. Which of the following matches the infectious agent with the correct mechanism of infection?

    (a) Fungi, indwelling infusion catheters
    (b) Gran-negative bacteria, breached mucosa of GI tract
    (c) Virus, indwelling infusion catheters
    (d) Gram-positive bacteria, indwelling infusion catheters

Correct Answer: B

Comments: Gram-positive bacteria infect through increased and prolonged use of indwelling infusion catheters. Fungal and viral infections are common in patients with prolonged neutropenia and a history of multiple chemotherapeutic uses.

14. True or False: The risk of fungal infection increases only with the duration and severity of neutropenia.

Correct Answer: False

Comments: Risk of fungal infection also increases with prolonged use of antibiotics and the number of chemotherapy cycles given.

15. 56 years old female with stage IIB ER/PR low positive and HER2 negative left breast cancer is undergoing dose dense AC (Adriamycin and cyclophosphamide) therapy in an adjuvant setting. After the second cycle, she visited emergency center with persistent fever of 39 °C over 2 h. She denies cough, chest pain, shortness of breath, diarrhea, or abdominal pain. She is receiving hydration and basic work ups. Which of the following belong to recommended basic work up?

    I. Blood and urine culture
    II. Comprehensive chemistry panel
    III. Chest X ray
    IV. Arterial blood gas analysis

    (a) I and II
    (b) I and III
    (c) II and III
    (d) I, II, and III

Correct Answer: D

Comments: Arterial blood gas analysis does not apply in this scenario given her negative respiratory symptoms. Basic work ups include blood and urine culture, chest X ray, complete blood count, and comprehensive chemistry panel.

16. Same patient from question #15, is complete with basic blood work. Her absolute neutrophil count is around 750 K/μL. The emergency center resident calls you to ask for a guidance on the choice of antibiotics. She has a medi-port to receive chemotherapy. Otherwise, physical exam is unremarkable except mucositis, and the surgical wound from her lumpectomy is well healed. Patient reports a penicillin allergy. Which antibiotics would you recommend?

    I. Cefepime 2 g IV q8h
    II. Piperacillin-tazobactam 4.5 g IV q6h
    III. Vancomycin 15 mg/kg IV q12h
    IV. Flagyl 500 mg IV q8h

    (a) I and II
    (b) I and III
    (c) II and III
    (d) I, II, and III

Correct Answer: B

Comments: While both cefepime and piperacillin-tazobactam can be first choice of gram-negative coverage, the patient has a penicillin allergy which makes the cefepime as a first choice. There could be a still cross-reactivity between penicillin allergy and cefepime. Since the patient has a mucositis, and risk of catheter-mediated infection, additional gram positive coverage with vancomycin is recommended.

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