Febrile neutropenia (FN) is an oncological emergency and serious complication often resulting from chemotherapy. In patients with a weak or completely suppressed immune system, a fever may be the only sign of an underlying infection and immediate treatment is needed. Using risk evaluation scores, it is possible to stratify individual patient degree of risk. However, all patients warrant immediate antibiotic coverage. Antibiotic treatment of FN is broadened or narrowed based on individualized clinical scenarios. Prophylactic antimicrobials may be used in specific high-risk situations. This article briefly reviews FN, describes risk assessment tools, and discusses treatment and prophylactic options.

INTRODUCTION

Febrile neutropenia (FN) is a serious complication often associated with cancer chemotherapy. Bone marrow suppression is the most common dose-limiting toxicity of traditional cytotoxic chemotherapy agents and has also been observed with targeted and immunotherapeutic therapies. Consequences of FN can include dose reductions, treatment delays, and substantial impact on morbidity and mortality. Findings from a study across inpatient and outpatient care settings demonstrated a 16.8% risk of developing FN during a course of chemotherapy. The Infectious Diseases Society of America defines neutropenia as an absolute neutrophil count (ANC) of 500 cells/mm³ or less with an anticipated decline to less than 500 cells/mm³ within 48 hours. Others define ANCs of less than 1,000 cells/mm³ or 500 cells/mm³ as moderate or severe neutropenia, respectively. Neutropenic patients are at increased risk of developing serious infections. FN is described by clinical practice guidelines as neutropenia with a single oral or tympanic temperature greater than or equal to 101°F (38.3°C) or greater than or equal to 100.4°F (38°C) for at least one hour.2–5

Neutropenia can result as a consequence of bone marrow injury either due to the cancer itself, chemotherapy and radiation, other underlying disease processes, or a combination of events. The release of endogenous cytokines by epithelial cells can cause fever during neutropenia. Barriers and mucosal linings in the body, including those in the gastrointestinal tract and sinuses, provide host defense against pathogens. Damage to the host barriers by chemotherapy and radiation along with potential organism access through central venous lines can lead to microbial invasion. Because the patient is neutropenic, typical signs and symptoms of infection, such as warmth and swelling, may not be present. Given the sustained inflammatory response with fever resulting from mucosal barrier injury, it is not always clear whether infection is the true underlying cause. The infectious etiology will not be determined in most cases; clinically documented infections occur in up to 30% of episodes, with even less microbiologically documented.

Many patients with FN may have an established or occult infection. Initially, infections tend to be primarily bacterial, but they could be fungal or viral. Common bacterial pathogens in immunocompromised patients include gram-positive bacteria, such as coagulase-negative staphylococci, Staphylococcus aureus, Enterococcus species, and Streptococcus species. The use of indwelling catheters has led to higher frequency of gram-positive bacterial infections. More recently, drug-resistant gram-negative organisms including Pseudomonas aeruginosa, Acinetobacter species, Stenotrophomonas maltophilia, Escherichia coli, and Klebsiella species have been identified as etiologic agents. Fungi such as Candida species or Aspergillus species have been more likely encountered after prolonged neutropenia and administration of broad-spectrum antibiotics. Subsequent infections may be caused by antibiotic-resistant bacteria, fungi, or viruses.

The consequences of febrile neutropenia are varied; many patients may receive antibiotics and have no further incident, but others may have life-threatening infections. At minimum, the resulting chemotherapy dose reductions and delays may impact the curative potential of treatment. In the metastatic setting, data from a retrospective health care claims study of more than 15,000 adults undergoing treatment demonstrated febrile neutropenia occurrence in up to 20%. Most were hospitalized, with a median length of stay of 7–7.5 days and mean costs of up to $19,456. Therefore, providers attempt to stratify patients at presentation into those at higher risk for infections.

PATIENT EVALUATION AND RISK ASSESSMENT

Because there is uncertainty about underlying infectious causes and potential clinical severity, several national consensus expert groups provide guidance for the initial risk assessment of patients presenting with FN (Table 1). Risk categorization correlates to the risk of serious medical complications, including mortality, and is used to determine treatment setting (inpatient versus outpatient), empiric antibiotic therapy (oral versus intravenous [IV]), and duration of antibiotic therapy. Patients at higher risk are more likely to experience a severe infection.

The Multinational Association for Supportive Care in Cancer (MASCC) risk index score was developed to identify patients with FN at low risk of serious medical complications or death. The MASCC score uses identifiable characteristics at the onset of FN to predict low risk of complications and the potential for successful outpatient management (Table 2). The scoring

ABSTRACT

Febrile neutropenia (FN) is an oncological emergency and serious complication often resulting from chemotherapy. In patients with a weak or completely suppressed immune system, a fever may be the only sign of an underlying infection and immediate treatment is needed. Using risk evaluation scores, it is possible to stratify individual patient degree of risk. However, all patients warrant immediate antibiotic coverage. Antibiotic treatment of FN is broadened or narrowed based on individualized clinical scenarios. Prophylactic antimicrobials may be used in specific high-risk situations. This article briefly reviews FN, describes risk assessment tools, and discusses treatment and prophylactic options.

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points from each criterion met by the patient are added to produce a final score. Results from the initial validation set found that a MASCC score of ≥ 21 identified low-risk patients with a positive predictive value of 91%, specificity of 68%, and sensitivity of 71%. Since the development of the MASCC risk index score, several validation studies have been published, all with a positive predictive value greater than 83%. The validation studies also showed a higher (greater than 90%) positive predictive value when fewer patients with hematologic malignancies were enrolled. This finding indicates the need for additional caution when using the MASCC score in patients with a hematologic malignancy.

The Clinical Index of Stable Febrile Neutropenia (CISNE) is an emerging prognostic score for predicting serious complications in outpatients with solid tumors and stable FN episodes (Table 3). The CISNE score identifies six variables associated with serious complications and classifies patients into three prognostic classes: low (0 points), intermediate (1–2 points), and high risk (3 points or more). The results of a multicenter validation study suggest the CISNE score may be more accurate than the MASCC score. A retrospective cohort study was conducted to compare the predictive accuracy of MASCC and CISNE scores in patients with FN presenting to the emergency department (ED). Results of this study indicate that the CISNE score was more specific for identification of the low-risk cohort and may be the more appropriate risk-stratification tool in the ED. The CISNE scoring system is not recommended in patients presenting with acute organ failure, clinical decompensation, or septic shock, or if a previously known severe infection is present.

MANAGEMENT

A neutropenic patient presenting with a fever is an oncological emergency and must be treated immediately. Cultures should be drawn, one from each lumen of a central line and one peripheral culture or two peripheral cultures if a central line is not present. If clinically indicated, cultures or x-rays may be obtained from other suspected sites of infection. The MASCC score can be used to determine whether a patient is
high or low risk. A low-risk patient may potentially be given oral antibiotics for treatment, but inpatient admission and IV antibiotics are indicated for high-risk patients. However, clinical discretion is advised based on the severity of a neutropenic patient’s infection. A short inpatient admission to receive IV antibiotics may be indicated initially even when the patient is deemed low risk. In all cases, treatment should be continued until the ANC is 500 cells/mm³ or greater and the patient is afebrile for at least 48 hours. Otherwise, the choice of antimicrobial therapy and duration should meet standard treatment length for any documented infection (i.e., pneumonia, urinary tract infection) or previous history of resistant organisms.3,5

Low-risk patients can be selected carefully for outpatient antibiotics, but they must be monitored very closely for clinical deterioration and must be located within a reasonable distance to a hospital in case one is needed. First-line options include fluoroquinolone (FQ) monotherapy, such as moxifloxacin or ciprofloxacin in combination with amoxicillin/clavulanic acid or clindamycin in place of amoxicillin/clavulanic acid in penicillin-allergic patients.3,5 If a patient remains febrile for 48 hours, antibiotic coverage should be broadened, and the patient will need to be admitted to the hospital.3

High-risk patients are admitted and will need to receive an antipseudomonal beta-lactam agent, such as cefepime, piperacillin-tazobactam, meropenem, or imipenem-clastatin.3,5 Institutional susceptibility patterns should be considered when selecting therapy. Pseudomonas is a main target during initial empiric therapy. Empiric coverage specifically directed at gram-positive organisms is not routinely recommended unless there is an underlying clinical indication.3,5 Vancomycin is recommended as empiric treatment for specific indications, including skin/soft tissue infections, pneumonia, catheter-related infections, or hemo-dynamically unstable patients.3 If vancomycin was initiated and no bacterial indication was documented within three days, it should be discontinued.3,5 Coagulase-negative staphylococci are the most commonly identified cause of bacteremia in neutropenic patients and typically do not cause rapid deterioration, so more serious gram-negative pathogens are targeted.3 In patients who do not respond to the initial therapy, antimicrobial coverage should be broadened to include resistant gram-negative/positive pathogens, anaerobic bacteria, and fungi (Table 4).3,5 Treatment for viral pathogens can be added if there is clinical indication.3

Empiric antifungal treatment should also be considered if a patient has a persistent fever for four days after initiation of therapy.3,5 If the patient presented to the hospital without antifungal prophylaxis, then Candida is likely and can be treated with fluconazole. However, patients who required fungal prophylaxis and then experienced FN are at risk for fluconazole-resistant fungi (C. krusei or C. glabrata) or an invasive mold infection (Aspergillus). If a resistant Candida strain is suspected, then an echinocandin, such as caspofungin, is recommended.3,5 A halo sign on chest computed tomography or a positive galactomannan test may help determine an Aspergillus infection, but a negative galactomannan test is not diagnostic due to low sensitivity. If Aspergillus is suspected, voriconazole would be an appropriate choice for empiric therapy, with escalation to amphotericin B if needed.5

In addition to antibiotics, a myeloid growth factor (MGF) regimen may be part of a treatment plan for select patients; several agents, including a biosimilar, are on the market (Table 5). The use of MGFs in the treatment setting continues to be an area of controversy. Results from a meta-analysis of 13 studies evaluating MGFs in addition to antibiotics in patients with established FN demonstrated decreased time of IV antibiotics and hospital length of stay, but no change in overall survival.16 National consensus expert groups recommend continuation of MGF in individuals who had already been receiving daily MGF treatment and consideration of adding an MGF to antibiotics only in individuals with risk factors for infection-associated complications. Possible indications include sepsis syndrome, ANC less than 100 cells/mm³, pneumonia, invasive fungal infection, or a patient who had experienced FN previously.17 Otherwise the addition of an MGF is not the standard of care in managing an FN episode.

**PREVENTION**

Preventive measures for infection are taken in cancer patients; hand washing is the single most important nonpharmacological step. Other options may include antimicrobials directed toward bacterial, viral, and fungal pathogen prophylaxis or stimulation of neutrophil production via MGF. The decision to initiate prophylactic antimicrobials is based on the individual’s risk of infection, which is elevated if a patient is expected to have profound neutropenia (defined as an ANC of 100 cells/mm³ or less for more than seven days) or anticipated neutropenia for more than 10 days.3,5 To determine the likelihood of pro-

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**Table 4 Treatment Options for Resistant Pathogens**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Antibiotic Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin-resistant <em>Staphylococcus aureus</em></td>
<td>Vancomycin, linezolid, daptomycin</td>
</tr>
<tr>
<td>Vancomycin-resistant <em>Staphylococcus aureus</em></td>
<td>Linezolid, daptomycin</td>
</tr>
<tr>
<td>Extended spectrum beta-lactamases</td>
<td>Carbapenems (meropenem)</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em> carbapenemase</td>
<td>Tigecycline, colistin</td>
</tr>
</tbody>
</table>

**Table 5 FDA-Approved Myeloid Growth Factors**

<table>
<thead>
<tr>
<th>Product</th>
<th>How Supplied and Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim (Neupogen, Amgen)</td>
<td>Vial and prefilled syringe; IV infusion or SC injection</td>
</tr>
<tr>
<td>Filgrastim-sndz (Zarxio, Sandoz)</td>
<td>Prefilled syringe; SC injection</td>
</tr>
<tr>
<td>Tbo-filgrastim (Granix, Cephalon)</td>
<td>Prefilled syringe; SC injection</td>
</tr>
<tr>
<td>Pegfilgrastim (Neulasta, Amgen)</td>
<td>Prefilled syringe and on-body injector; SC injection</td>
</tr>
<tr>
<td>Sargramostim (Leukine, Partner Therapeutics)</td>
<td>Vial; IV infusion or SC injection</td>
</tr>
</tbody>
</table>

* Biosimilar to Neupogen.

FDA = Food and Drug Administration; IV = intravenous; SC = subcutaneous.
Management and Preventive Measures for Febrile Neutropenia

found neutropenia, it is important to consider the type of malignancy and which medications are used. Hematologic malignancies inherently will cause prolonged neutropenia due to both the effects of the malignancy on the bone marrow in addition to myelosuppressive chemotherapy. Patients receiving a bone marrow transplant (BMT) require more specialized antimicrobial prophylaxis, and solid tumor malignancies may cause neutropenia if they spread to the bone marrow or if the patient receives intensive myelosuppressive chemotherapy. Once prophylaxis is initiated, it will be maintained until the patient is no longer neutropenic and started again if indicated.5

Antibacterial prophylaxis has caused substantial reductions in infection-related mortality in neutropenic patients and is recommended for high-risk patients as noted above.5,10 Results from a meta-analysis of 52 trials of neutropenic patients with primarily hematologic malignancies demonstrated the efficacy of FQs in prevention of bacterial infections without breeding resistant organisms.10 Levofloxacin is the recommended FQ based on national guidelines.5 Levofloxacin at high doses (500–750 mg) has a broader scope of coverage, in comparison to ciprofloxacin or moxifloxacin, by covering *Pseudomonas*, other gram-negative rods, and some gram-positive pathogens (including streptococci).5,10 In patients unable to take an FQ, trimethoprim/sulfamethoxazole (TMP/SMX) or a third-generation cephalosporin may be used.5

Viral prophylaxis with acyclovir is indicated in patients who are herpes simplex virus seropositive and likely to be neutropenic due to a risk of viral reactivation.5 In addition, patients who required treatment for a viral illness during prior therapy will require viral prophylaxis.5 Patients undergoing hematopoietic stem cell transplantation (HSCT) will have different needs for viral prophylaxis due to an increased risk for varicella zoster activation with the prolonged immunosuppression associated with treatment. For example, in the HSCT setting, acyclovir dosing is 800 mg by mouth twice a day (rather than 400 mg) and is continued until one year post-transplant or until immunosuppression is complete.20

Fungal prophylaxis is also indicated for patients at high risk for profound neutropenia, but differs in agents based on coverage for *Candida* or *Aspergillus*. Fluconazole is effective at decreasing fungal-related infections due to *Candida*, although other triazoles or echinocandins are alternatives.3,5 Patients with acute myeloid leukemia or myelodysplastic syndrome who are receiving chemotherapy are at an increased risk of invasive *Aspergillus* infections, and posaconazole has prevented more fungal infections and increased overall survival in this population.21 In other populations, such as HSCT patients, *Aspergillus* prophylaxis is not recommended unless patients have had a prior occurrence.3

MGFs prevent the risk of FN by boosting the patient’s immune system, increasing production of neutrophils to combat the myelosuppressive effects of chemotherapy. Common chemotherapy regimens are believed to cause profound neutropenia, and the addition of an MGF may be recommended with these regimens. As a general recommendation, if FN risk is 20% or greater with a chemotherapy regimen, an MGF should be used.17 Examples of chemotherapy regimens with greater than 20% risk include dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin), dose-dense AC with T (doxorubicin, cyclophosphamide, followed by paclitaxel), hyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone), VIP (etoposide, ifosfamide, cisplatin), and dose-dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin).17 FN risk between 10% and 20% is deemed intermediate risk, and MGF use is determined by provider preference based on individual patient risk factors, such as age, coexisting conditions, and prior chemotherapy.17 Chemotherapy regimens for acute leukemia are highly myelosuppressive; however, use of MGF in these populations is limited to specific protocols and circumstances. There is concern about promoting the growth of malignant cells being produced within the bone marrow. In addition, the timing of MGF administration may confound results of bone marrow biopsy interpretation.22

Allogeneic HSCT patients have a more complex regimen of antimicrobial prophylaxis due the removal of the host immune system and prolonged immunosuppression correlated with graft-versus-host disease. Viral prophylaxis is maintained for longer periods and at higher doses. Unlike other malignancies, allogeneic BMT patients have a high risk of cytomegalovirus (CMV) infections during the early post-engraftment phase and will require treatment if CMV-seropositive with valganciclovir.5 There is an increased risk of encapsulated organism infection in BMT patients after day 30, and up to one year post-transplant. TMP/SMX is used as a first-line therapy for encapsulated organism prevention, with dapsone and pentamidine as alternative therapies.23 Fungal prevention with fluconazole will be continued until immunosuppression treatments are completed. Ultimately, patients receiving HSCT will be on more prophylactic medications and have a longer duration of therapy compared with patients receiving conventional chemotherapy.

CONCLUSION

Febrile neutropenia is a life-threatening complication often associated with cytotoxic chemotherapy and malignancies that has a significant impact on morbidity and mortality. Utilizing the MASCC and CISNE risk criteria enables health care providers to categorize a patient’s risk for serious medical complications from infections. A patient is either high or low risk, which dictates initial therapy using an oral FQ for outpatient treatment or an IV antipseudomonal beta-lactam agent. Following guideline recommendations and studies published on FN management, empiric treatment may be broadened or narrowed as clinically indicated. Ultimately, it is important to know whether a patient is expected to be at high risk for developing FN or has a history of FN, as prophylactic measures can be taken. Understanding FN and the process of treating or preventing FN in the immunosuppressed population is an important step toward improving patient outcomes.

REFERENCES


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