Best Practices in the Management of Infectious Complications for Patients With Cancer: Management of Febrile Neutropenia

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Presenter's disclosure of conflict of interest is found at the end of this article.

https://doi.org/10.6004/jadpro.2023.14.3.4

Abstract

Managing infection in patients with neutropenia is a difficult challenge, as fever is often the only clinical symptom. At JADPRO Live 2022, Kyle C. Molina, PharmD, BCIDP, AAVHIP, of the University of Colorado Hospital, discussed the epidemiology and pathophysiology associated with febrile neutropenia in patients with cancer. He reviewed appropriate treatment settings and empiric antimicrobial regimens for a patient and how to formulate a plan to safely de-escalate and target therapy for patients with febrile neutropenia.

Febrile neutropenia, a life-threatening condition characterized by fever and low neutrophil count, places a significant burden on both patients and the health-care system. Although the incidence of febrile neutropenia varies by malignancy, between 10% and 50% of patients with solid tumors and at least 80% of patients with a hematologic malignancy will develop the condition (Klastersky, 2004).

During JADPRO Live 2022, Kyle C. Molina, PharmD, BCIDP, AAVHIP, of the University of Colorado Hospital, described the epidemiology and pathophysiology associated with febrile neutropenia in patients with cancer and discussed appropriate empiric antimicrobial regimens. Dr. Molina also compared and contrasted escalation with de-escalation approaches in the management of febrile neutropenia.

EPIDEMIOLOGY OF FEBRILE NEUTROPENIA

Febrile neutropenia is a condition in which a patient with neutropenia (an absolute neutrophil count [ANC] below 500 cells/µL or an ANC of less than 1,000 cells/µL expected to fall within the next 48 hours to below 500 cells/µL) also has a fever (an oral temperature of 38.3°C or two

J Adv Pract Oncol 2023;14(3):201–206

temperatures of 38°C for over an hour). According to Dr. Molina, it is important to consider the individual patient and other factors, such as medications that may blunt the immune and cytokine response, when making the diagnosis.

"In the past 20 years, the incidence of febrile neutropenia has decreased due to advances in chemotherapy and supportive care," said Dr. Molina. "However, it is still a significant concern for patients with hematologic malignancies, as they have a higher risk of developing the condition."

To assess the risk of febrile neutropenia in an individual patient, it is necessary to consider patient-related factors (such as age and comorbidities), disease-related factors (such as tumor burden and hematologic derangements), and treatment-related factors (such as the type and duration of chemotherapy).

The National Comprehensive Cancer Network (NCCN) has developed a stratification of risk based on treatment factors. High-risk patients include those with acute leukemias receiving high-dose chemotherapy, while moderate-risk patients include those with chronic lymphocytic leukemia, lymphoma, or multiple myeloma receiving certain types of chemotherapy (NCCN, 2022). Low-risk patients include those with neutropenia lasting fewer than 7 days and those with solid tumors.

Patients with febrile neutropenia may be treated with broad-spectrum therapies such as fluoroquinolones or carbapenems, which can be expensive, difficult to administer, and require invasive central lines. These patients may need to be hospitalized for over 2 weeks and have a daily estimated cost of over $1,500. The mortality rate for patients with febrile neutropenia is up to 10%, and the condition can also lead to other morbidities.

MICROBIOLOGY OF FEBRILE NEUTROPENIA

As Dr. Molina reported, data from a study at The University of Texas MD Anderson Cancer Center found that in 50% of patients with febrile neutropenia, an infectious source can be identified, including 25% with microbiologically documented infections and 25% with clinically documented infections (Freifeld et al., 2011). An additional 3% to 5% of cases have noninfectious etiologies such as drug fever or cytokine release syndrome. The remaining 45% of patients do not have a clear cause of fever.

Another study from MD Anderson Cancer Center found that 57% of bloodstream infections in these patients were caused by gram-negative organisms, 33% were caused by gram-positive organisms, and 10% were polymicrobial (Klastersky et al., 2007). However, respiratory tract infections are the most common type of infection in patients with febrile neutropenia, and gram-positive organisms are more common in these infections, said Dr. Molina.

Overall, gram-positive organisms are responsible for 60% of infections in patients with febrile neutropenia. In addition to respiratory tract and bloodstream infections, urinary tract infections and skin and skin structure infections are also common in these patients.

MASCC SCORE

When a patient presents with febrile neutropenia, it is important to assess their risk of complications using the MASCC (Multinational Association for Supportive Care in Cancer) score, which considers factors such as the severity of symptoms, age, the presence of underlying conditions (such as chronic obstructive pulmonary disease), and type of cancer (Figure 1).

Patients who are at low risk for complications may be treated on an outpatient basis with oral antibiotics, while patients who are at moderate risk may be hospitalized for a short period and given intravenous (IV) antibiotics before being discharged with oral medication. High-risk patients will be treated with inpatient IV antibiotics.

"It is important to give the first dose of antibiotics to patients with febrile neutropenia within 1 hour, and to observe the patient for at least 4 hours to determine if the initial IV antibiotic is effective," said Dr. Molina. "If the patient remains stable, they may be discharged with a fluoroquinolone-based regimen or a combination of fluoroquinolone and amoxicillin-clavulanate."

THE EVOLUTION OF ANTIBIOTICS TO TREAT FEBRILE NEUTROPENIA

According to Dr. Molina, the evolution of antibiotics over the past several decades has influenced the microbiology of febrile neutropenia. In the

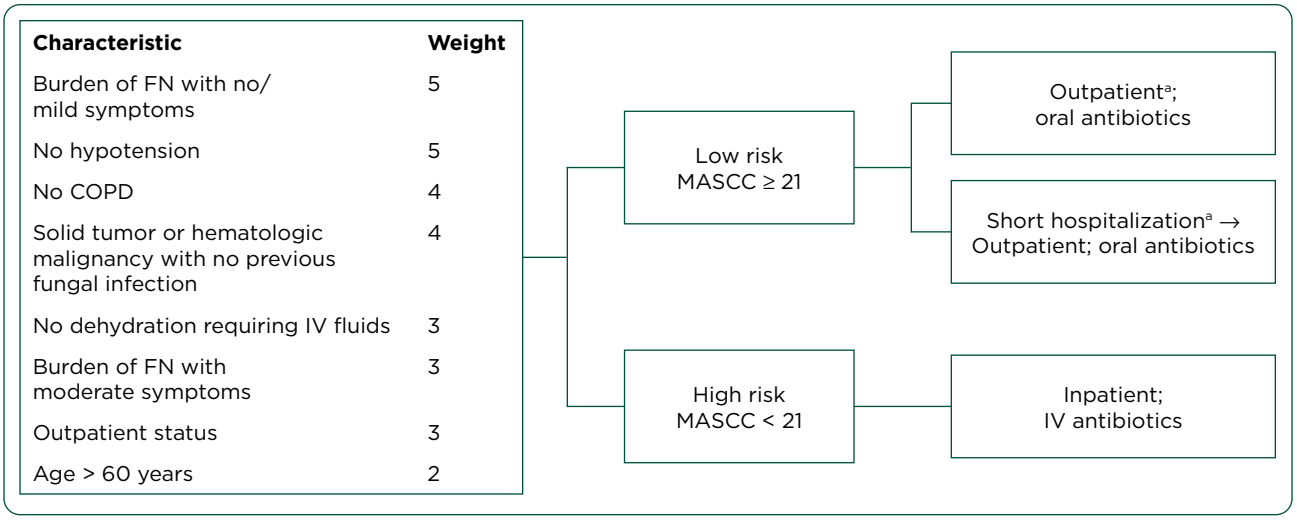

Figure 1. Risk assessment for complications: MASCC score. FN = febrile neutropenia; COPD = chronic obstructive pulmonary disease; MASCC = Multinational Association for Supportive Care in Cancer. Information from Freifeld et al. (2011).
[a]Depends on Clinical Index of Stable Febrile Neutropenia (CISNE) score.

past, penicillin and cephalexin were commonly used to treat infections, but these drugs had limited ability to cover gram-positive and pseudomonas infections. The introduction of fluoroquinolones and beta lactamase inhibitors in the 1970s and 1980s expanded the range of infections that could be treated, leading to a shift toward gram-positive organisms *Staphylococcus aureus* and coagulase-negative *Staphylococcus*, which now make up about 60% of pathogens in febrile neutropenia. More recently, the use of extended spectrum cephalosporins, carbapenems, and fluoroquinolone prophylaxis has led to an increase in the prevalence of multidrug resistant (MDR) gram-negative organisms.

"The increase in MDR gram-negative organisms has made it more challenging to choose appropriate empiric therapies and has increased the importance of considering an individual patient's risk of resistant infections," said Dr. Molina. "It has also become necessary to consider combination therapies and newer broad-spectrum therapies in order to cover resistant organisms."

"We're continuing to race against these microorganisms, and it is an uphill battle," he added.

INPATIENT MANAGEMENT IN THE ERA OF MDR

In the era of MDR organisms, there are two main approaches in the management of patients with febrile neutropenia: escalation and de-escalation. Escalation refers to starting with a narrow spectrum of antimicrobials and gradually increasing the spectrum based on the patient's clinical response. According to Dr. Molina, this approach is suitable for patients with an uncomplicated presentation, such as those who are hemodynamically stable and have not been exposed to many antimicrobials in the past (Figures 2 and 3).

On the other hand, de-escalation refers to starting with a broad spectrum of antimicrobials and gradually narrowing the spectrum based on the patient's clinical response. This approach is suitable for patients with a complicated presentation, such as those with severe sepsis or septic shock, or those who have recently been colonized or infected with MDR organisms.

"The choice between escalation and de-escalation should be tailored to the individual institution and its prevalence of MDR," said Dr. Molina.

For patients with a relatively uncomplicated presentation and low risk of colonization with resistant organisms, a relatively narrow-spectrum antibiotic such as cefepime may be used initially and then broadened if necessary. However, if the institution has a high prevalence of resistance to cefepime, a carbapenem may be needed even for uncomplicated patients. For patients with severe sepsis or septic shock, broad initial therapy is recommended, particularly if the patient has recently

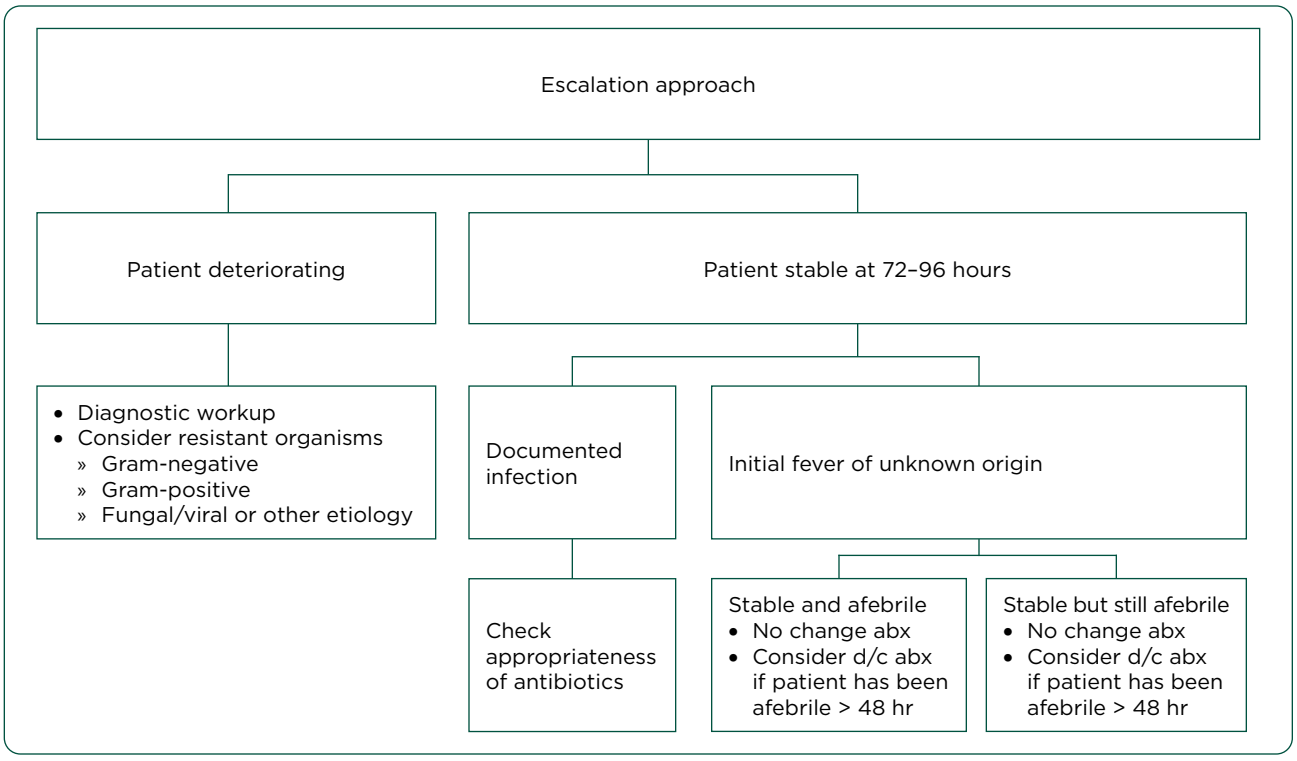

Figure 2. Escalation approach. Abx = antibiotics; d/c = discontinue. Information from Averbuch et al. (2013).

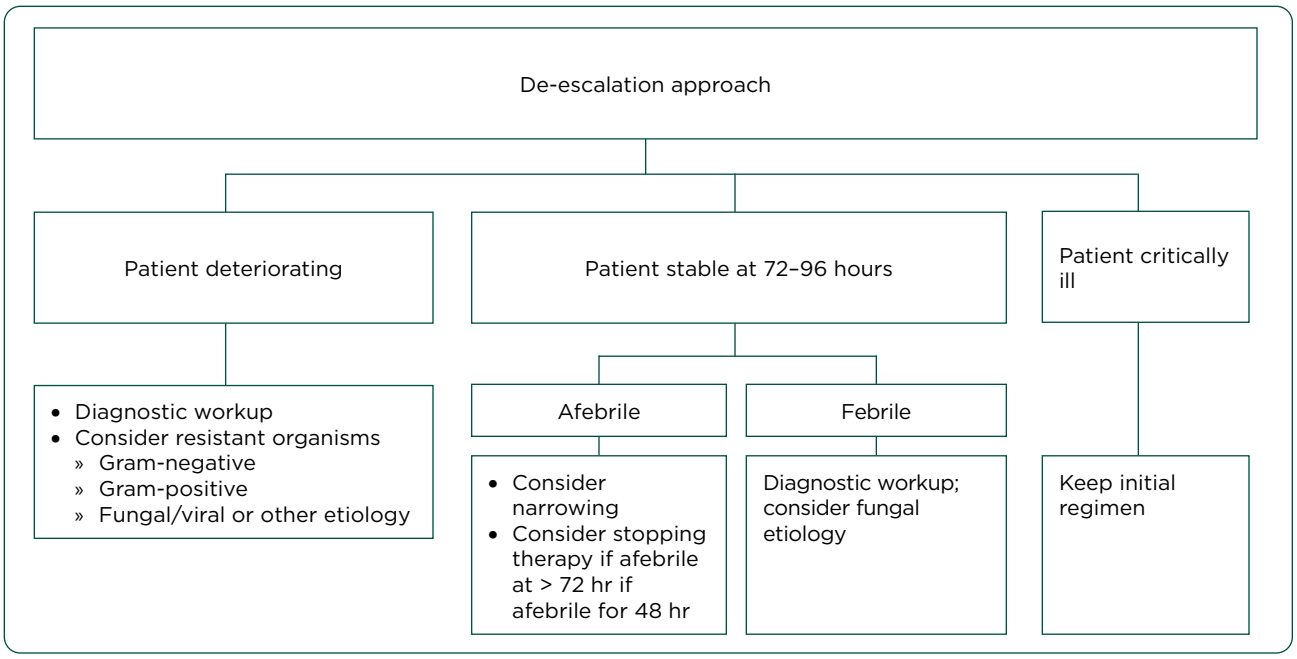

Figure 3. De-escalation approach. Abx = antibiotics; d/c = discontinue. Information from Averbuch et al. (2013).

been colonized or infected with a resistant organism or if the institution has a high prevalence of resistance to carbapenems and other important antibiotics. De-escalation, or the reduction of antibiotic coverage, can then be considered once the patient's condition improves.

One study of risk factors for shock and death in over 1,300 cases involving 826 patients found that shock is rare in patients with febrile neutropenia who are started on antibiotics, and death is even rarer (Guarana et al., 2019). Non-Hodgkin lymphoma, pneumonia, and shock were identified as risk factors for early death in the study, but adequate empiric therapy was shown to be protective against early death.

"Gram-positive organisms were not found to be risk factors for shock or death in the study, while gram-negative organisms were identified as risk factors," said Dr. Molina.

A meta-analysis of 11 studies also found that there is no difference in all-cause mortality between patients who receive empiric vancomycin and those who do not, but that there were more adverse events in patients who received vancomycin (Paul et al., 2005). Overall, the study suggests that adding vancomycin to empirical treatment regimens may not improve patient outcomes and may potentially harm them, supporting the escalation approach for most patients, said Dr. Molina.

OPTIONS FOR INITIAL INPATIENT ANTIMICROBIALS

When selecting an antimicrobial regimen for a patient, the first approach is to use cefepime, piperacillin-tazobactam, or carbapenem monotherapy, but this may not be effective at certain centers due to high rates of resistance among *Pseudomonas* bacteria. An alternative approach is to use combination therapies, such as aminoglycosides or quinolones. However, aminoglycosides can cause nephrotoxicity and quinolones may have been ineffective in the past for the patient.

Dr. Molina also noted the use of newer beta-lactam and beta-lactamase inhibitors (e.g., ceftazidime-avibactam, cefiderocol), which have broad-spectrum activity against resistant bacteria and are safer than aminoglycosides. According to Dr. Molina, it's important to consider the specific resistant organisms present at the patient's institution and adding coverage for resistant gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *enterococci*, as needed.

With respect to de-escalation, the Infectious Diseases Society of America recommends continuing the initial treatment regimen until the patient shows signs of marrow recovery, as indicated by an increasing ANC exceeding 500 cells/µL. In contrast, the European guidelines suggest that antibiotics may be safely discontinued after 72 hours in certain cases when an infection is not identified, even if the patient has not yet shown signs of bone marrow recovery.

CLINICAL TRIALS SUPPORTING DE-ESCALATION

Two landmark studies have explored de-escalation in different patient populations. The first study, called the "How Long" study, compared de-escalation to continued treatment in patients who had been afebrile for 72 hours and had an ANC greater than 500 cells/µL (Aguilar-Guisado et al., 2017). The study found that de-escalation was safe and resulted in fewer antibiotic days and fewer adverse events but did not affect mortality rates.

The second study, called the ANTIBIOSTOP study, compared de-escalation in patients who were afebrile for 48 hours to continued treatment for at least 5 days (Le Clech et al., 2018). The study found that unfavorable outcomes occurred at similar rates in both groups and that hospital mortality and the need for ICU admission were not statistically different.

Finally, a retrospective study of de-escalation in a real-world setting found that the strategy saved 2 days of therapy and did not affect rates of severe sepsis or mortality, although it did result in higher rates of bacteremia (Verlinden et al., 2021). Infection-related mortality was higher in the control group.

"Overall, the results of these studies suggest that de-escalation is a safe and effective strategy for reducing treatment durations in patients with febrile neutropenia when no infectious etiology is identified," said Dr. Molina.

According to Dr. Molina, de-escalation is important to reduce the risk of *C. difficile* infection in patients undergoing chemotherapy, reduce

the risk of additional antimicrobial resistance, and reduce the risk of potential complications such as rashes and nephrotoxicity. Despite these benefits, however, a recent survey of cancer centers found that a large proportion of these centers did not have explicit guidance for clinicians on when to consider de-escalating therapy (Barreto et al., 2022).

"It's important to be explicit in protocols and consider implementing strategies to reduce the duration of antibiotic therapy in order to optimize patient outcomes," Dr. Molina concluded. ●

Disclosure

The presenter has no relevant financial relationships to disclose.

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