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Management of the febrile neutropenic patient in 2023

David-Valentin Mangaloiu[1], Isabela-Daniela Staicu[1], Anca Ruxandra Negru[1,2], Violeta Molagic[1,2], Catalin Tiliscan[1,2], Aida-Isabela Adamescu[1,2], Oana-Alexandra Ganea[1,2], Laurentiu-Mihaita Stratan[1,2], Nicoleta Mihai[1,2], Stefan Sorin Arama[1,2], Victoria Arama[1,2]

[1]"Prof. Dr. Matei Bals" National Institute for Infectious Diseases, Bucharest, Romania
[2]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Febrile neutropenia (FN) is a well-known complication of chemotherapy (CHT) regimens, which appears more frequently in patients receiving CHT for hematologic malignancies, than those with solid tumors. Given the fact that this condition is life threatening, as well as multiple complications that may happen, rapid intervention is required, administration of empirical antibiotic therapy being necessary in the first hour of admission.

Due to the high mortality rate associated with Pseudomonas aeruginosa infections, patients at risk should be given an antipseudomonal antibiotic agent, such as cefepime, carbapenem or piperacillin-tazobactam. Regarding empirical antibiotic coverage for gram-positive microorganisms, this is preserved for hypotensive patients, with skin/soft infections or suspected catheters infection or those taking fluoroquinolone.

Considering the fact that a variety of bacterial, viral and fungal pathogens are responsible for high morbidity and mortality among patients with FN, preventable measures like antibiotic, antifungal and antiviral, as well as vaccination and prophylaxis with G-CSF, are crucial components in providing medical treatment for onco-hematological patients.

Keywords: febrile neutropenia, onco-hematologic patients, infections, chemoprophylaxis

INTRODUCTION. DEFINITIONS

Infections represent an important cause of morbidity and mortality in patients with malignancies. Neutropenia is considered a major risk factor for developing infectious diseases in patients with cancer undergoing chemotherapy (CHT) [1]. The decrease in the absolute neutrophil count following CHT leads to a reduction in the body's capacity to fight pathogenic microorganisms [2]. Neutrophils are the main cells involved in antimicrobial defense, especially in the fight against bacterial and fungal infections. The longer duration and the larger depth of neutropenia, the greater the risk of infection, with the highest risk in patients who manifest profound and prolonged neutropenia after CHT, most likely occurring prior to engraftment in hematopoietic stem-cell transplantation or subsequent to induction CHT in the case of acute leukemia [3,4].

Fever is an important sign and often the only indicator of neutropenia. However, clinicians should take into consideration the fact that patients with profound or severe neutropenia can also present with a suspected infection even in afebrile state or hypothermia [4].

Neutropenia is defined as a decrease in the absolute neutrophil count (ANC) <1.000 cells/μL (equivalent to $<1.0 \times 10^9$/L) [3]. Severe neutropenia is defined as a decrease of ANC <500 cells/μL or if expected to decrease <500 cells/μL in the next 48 hours [4,5]. Profound neutropenia is defined as ANC <100 cells/μL [3].

Corresponding author:
David Valentin Mangaloiu
E-mail: mangaloiudavid@gmail.com

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Febrile neutropenia (FN) is defined as an oral temperature >38.3°C or two consecutive readings >38.0°C during a 2-hour period and an ANC <0.5 × 10^9/L or expected to decrease below 0.5 × 10^9/L [6].

EPIDEMIOLOGY, MORBIDITY AND MORTALITY

Infections lead to a significantly increased morbidity and mortality in patients with cancer, with an up to 10 times higher mortality risk from sepsis, than patients without malignancies. Therefore, detecting active or latent infections is essential before initiating CHT, administering antimicrobial prophylaxis and vaccinations [7].

Prevention and adequate management of febrile neutropenic patients is essential because of the risk of major complications that can occur: hypotension, acute heart, renal or respiratory failure, disseminated intravascular coagulation, major bleeding, arrhythmia and altered mental status. The rate of complications varies between 25% and 40%, with the mortality rate up to 11%. Hospital mortality in case of sepsis or septic shock can be up to 50% [4].

Febrile neutropenia is a frequent and severe complication of CHT. It occurs in up to 80% of patients with hematological malignancies and 10-50% of patients with solid tumors receiving CHT [8]. After CHT, most patients experience a 6 to 8 days course of neutropenia and 8 cases per 1000 patients will develop FN [6].

There is a strong relationship between the severity of the neutropenia (which directly influences FN incidence) and the CHT intensity. Nowadays, the regimens are divided by the risk of FN that they cause: high risk (>20%), intermediate risk (10-20%) or low risk (<10%]. Western countries reported a mean cost of hospitalization of approximately 13.500 € (15.000 $) [6].

Risk factors that predispose onco-hematological patients to infectious complications.

The following are the main causes of an infection in onco-haematological patients requiring CHT, according to *National Comprehensive Cancer Network (*NCCN): neutropenia, impaired integrity of mucosal barriers- sinopulmonary, gastrointestinal and genitourinary; functional asplenia or splenectomy - risk of infections with encapsulated bacteria, such as *Streptococcus pneumoniae, Haemophilus influenzae* or *Neisseria meningitidis;* immunodeficiency associated with primary malignancy; autologous or allogeneic hematopoietic cell transplant; use of corticosteroids or other immunosuppressive therapies, tumor obstruction, presence of central venous catheters, advanced age, male patients, comorbidities, genetic factors and nutrition [1].

MICROORGANISMS INVOLVED IN FEBRILE NEUTROPENIA

FN is caused commonly by bacteria, but viruses and fungi can also be involved. Over the last decades, FN etiology has changed, Gram-positive cocci being responsible for more infections than Gram-negative bacilli (GNB) [1,9]. Research conducted by the *Multinational Association for Supportive Care in Cancer (MASCC)* involving 2142 patients with neutropenic fever secondary to CHT, showed that bacteraemia was identified in 23% of the patients, Gram-positive bacteria being involved in 57% of the cases, Gram-negative bacteria in 34% of the cases and multiple bacteria were identified in 10% of the cases [10].

The most frequent Gram-positive pathogen involved is *Staphylococcus epidermidis*, being responsible for approximately half of the Gram-positive infections and with lower virulence than other bacterial pathogens. *Staphylococcus aureus* (especially methicillin-resistant strains), *Streptococcus viridans* and *Enterococcus* spp. (especially vancomycin-resistant strains) can cause serious infections in the Gram-positive group [11].

Gram-negative bacteria are generally associated with the most severe infections, especially *Pseudomonas aeruginosa*. The most commonly detected species causing infections in FN patients are: *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* [12].

In a study that took place in Brazil, between 2012 and 2021, which described the microorganisms causing blood stream infections (BSI) in individuals over 18 years old who had received systemic CHT for solid or hematological malignancies, GNB where the etiological agents in 35.5% BSI episodes (537 out of 1512 blood cultures), from which 17.3% were carbapenem-resistant. In this study, the most common pathogen isolated was coagulase-negative *Staphylococcus* (40.1%), followed by *Escherichia coli* (13.2%), *Staphylococcus aureus* (11.8%), *Klebsiella* spp. (8.7%), *Pseudomonas aeruginosa* (5.2%) [13].

Although bacteria are frequently the cause of FN, fungal infections became more frequent with an incidence that varies between 2 and 36.5%, having a high risk of complications [14,15]. *Candida* spp. and *Aspergillus* spp. are responsible for most invasive fungal infections in neutropenic patients. *C. albicans* is the principal cause of candidemia, as well as other non-albicans species. *Candida* spp. is frequently associated with central venous catheter infections and can cause disseminated candidiasis. Other incriminated fungi are *Fusarium* spp., *Histoplasma capsulatum*, *Coccidioides spp*. and *Blastomyces dermatitidis* [14].

Regarding patients with solid tumors, they rarely develop invasive fungal infections (< 8%), especially those who have risk factors like: previous antibiotic use, history of receiving multiple CHT lines, high-

dose corticosteroids (equivalent or over 20 mg prednisone per day for 4 weeks or more), prolonged neutropenia (>7 days), extensive mucositis or the presence of a central venous catheter [11].

Viruses are can also cause FN, especially upper and lower respiratory tract infections, which are more severe than in immunocompetent individuals. *Adenovirus*, *metapneumovirus*, *influenza* and *parainfluenza virus* and *respiratory syncytial virus*, as well as *SARS - CoV - 2* virus can be involved. Other viruses that can cause FN are: *herpes simplex virus 1 and 2, varicella zoster virus (VZV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV)* [14,16]

The etiological agent is identified (microbiological documentation) in only 20-30% of the cases, while positive blood cultures can be found in only 10-25% of the patients. Bacterial etiology is usually present, both Gram-negative bacilli and Gram-positive cocci being isolated, with ratio of 3:2. Polymicrobial infections or anaerobic microorganism are a less common etiology, occurring in certain situations (for example, abscesses or enteritis]. An increase in the strains resistant to carbapenemases or extended-spectrum β-lactamase (ESBL) has been observed in recent years. Incidence of resistant pathogens depends on prior colonization, hospitalization, exposure to antibiotics, local resistance pattern, invasive procedures and comorbidities [1,17].

INITIAL EVALUATION AND INVESTIGATIONS OF THE FEBRILE NEUTROPENIC PATIENT

A detailed history including the fever onset, type of CHT administered, recent antibiotic prophylaxis, concomitant corticosteroid treatment, comorbidities, recent surgical procedures and allergy history is mandatory [6].

In order to guide the treatment, it is essential to check previous clinical records for prior positive microbiological documentations, especially previous findings of antibiotic-resistant pathogens and bacteremia. Initial evaluation should check respiratory and circulatory functions, followed by comprehensive examination for potential sources of infection (skin and oropharynx inspection, sinus palpation, pulmonary auscultation, abdomen palpation, perineal examination, any indwelling catheters and recent venipuncture sites) [6,12].

Patients with FN can have minimal signs and symptoms of infection, particularly elderly who may often present with confusional states or patients receiving corticosteroid treatment. Patients with critical condition, hypotensive, in afebrile state or hypothermia, are at high risk of developing Gram-negative sepsis [6,12].

Initial investigations include urgent blood count to assess the absolute neutrophil count, renal and liver blood tests, coagulation screen, C-reactive protein, procalcitonin, minimum two sets of blood cultures from peripheral vein and indwelling intravenous catheter, microbiological testing from suspected sites of infection (sputum microscopy and culture, urinalysis and culture, stool microscopy and culture, nasopharyngeal swab, skin lesion swab), before administering empirical broad-spectrum antimicrobial treatment and, if possible, catheter removal. Chest radiograph is mandatory during initial assessment and further imaging should be performed depending on the clinical suspicion [6,12,15].

Most common sites of infection in patients with FN include the site of venous catheter insertion, skin, oral cavity, gastrointestinal or genitourinary tract and respiratory system [9]. Urinary tract infections must be suspected even in asymptomatic neutropenic patients with prior history of such infections [6].

RISK ASSESSMENT IN PATIENTS WITH NEUTROPENIC FEVER

The *Multinational Association for Supportive Care in Cancer (MASCC)* risk index score, published in 2000, is currently used for risk assessment in patients with FN. Its goal is to identify the patients who, on initial evaluation, are at low risk for severe development, complications and mortality. Early differentiation between patients at high risk and those at low risk for complications is useful in order to initiate a less extensive spectrum empiric antimicrobial schemes, administer oral or outpatient treatment. The score includes parameters such as: symptom severity, hypotension, history of chronic obstructive pulmonary disease, history of previous fungal infection, dehydration and age. Several studies have validated this algorithm, with sensitivity between 71-95% and specificity between 40-95%. In patients with MASCC score ≥21 who are considered to have low risk for complications may be taken into consideration, after initial assessment, outpatient management if they live within one hour distance from the medical institution, have an attendant at home and can quickly return in case of emergency or for follow-up [8,12]. The rate of medical complications in low risk patients is estimated at 6%, with a mortality rate under 1% [6].

The *Clinical Index of Stable Febrile Neutropenia (CISNE)* score was developed in 2015 and validated for predicting severe complications in FN patients with high-risk scores ≥3, unlike the MASCC risk index score which identifies low risk patients. The area under a receiver operating characteristic (ROC) curve obtained in the validation cohort for the MASCC score was 0.721 and 0.868 for CISNE score (p =

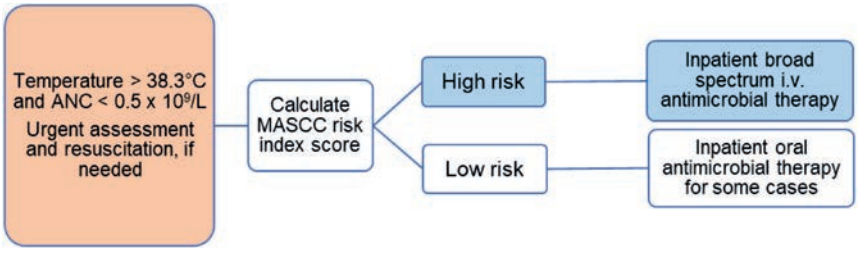

FIGURE 1. Initial management of FN- modified after ESMO Clinical Practice Guidelines 2016

.002]. There are advantages and also limitations for CISNE score: the validation trial enrolled only solid tumor patients who were normotensive and stable, without any element of clinical concern and who received mild to moderate CHT. Consequently, the CISNE score can only be used on this cohort [8].

RISK STRATIFICATION FOR FN PATIENTS

Patients with FN are divided into two categories corresponding on their risk, according to *National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO),* and *European Society for Medical Oncology (ESMO)* [1,3,6].

INITIAL EMPIRIC ANTIBIOTIC THERAPY

When an infection is suspected all neutropenic febrile patients should undergo rapid empirical treatment with broad-spectrum antibiotics, to prevent death from treatment-related delays. The following factors should be considered when choosing the initial treatments: risk of infection and the most common localizations, the local resistance profile (ESBL, VRE – vancomycin – resistant enterococci, MRSA - methicillin resistant *Staphylococcus aureus*), frequently occurring microorganisms implicated in infections, treatment regimens that cover *Pseudomonas aeruginosa*, hemodynamical instability, recent antibiotic therapy administered with a curative or prophylactic intent, and antibiotic allergies [1].

Patients with FN with a low risk of complications can be treated in an outpatient setting or in a hospital with oral or intravenous empirical antibiotics. Clinicians should take the decision to outpatient treatment based on clinical judgment, MASSC score and Talcott's criteria. Patients undergoing hematopoietic stem cell transplant (HSCT) or induction therapy for acute leukemia as well as those suspected of having MRSA, VRE, *Stenotrophomonas maltophilia*, or other infections with bacteria resistant to quinolones or β-lactams are not thought to be acceptable for outpatient management [4].

The antibiotic treatment recommended by the 4 guidelines presented in Table 2 is represented by monotherapy with quinolones or combination therapy with ciprofloxacin + amoxicillin / clavulanate. In case of allergies to β-lactams the preferred regimen is ciprofloxacin + clindamycin. Another unanimous recommendation of the below guidelines is that patients who have taken a quinolone antibiotic as prophylactic shouldn't be given oral quinolone medication [1,3,6].

TABLE 1. Stratification of the infection risk for patients with febrile neutropenia [1,3,6]

LOW RISK	HIGH RISK
❑ MASCC score ≥21; CISNE score <3	✓ MASCC score <21; CISNE score >3
❑ Anticipated short duration of severe neutropenia (<7 days)	✓ Anticipated prolonged severe neutropenia ≤100 cells/μL and duration ≥7 days
❑ No comorbidities	✓ Significant comorbidities* or clinically unstable patient
❑ No renal or hepatic insufficiency	✓ Allogeneic hematopoietic stem-cell transplant
❑ Development of fever during outpatient status	✓ Hepatic insufficiency (AST/ALT × 5 LSN)
❑ Good performance status (ECOG 0-1)	✓ Renal insufficiency (creatinine clearance <30 mL/min)
❑ Clinical judgment	✓ Uncontrolled/progressive cancer**
	✓ Pneumonia or serious infections at clinical presentation
	✓ Alemtuzumab
	✓ Mucositis grade 3-4
	✓ Clinical judgment

*Hemodynamically unstable, gastrointestinal tract symptoms, appearance of new neurological symptoms, catheter-related infections, chronic pulmonary disease, etc.

** Uncontrolled/progressive cancer is defined as any patient with leukemia not in complete remission or patients without leukemia with disease progression evidence after more than two courses of CHT.

Patients with a high risk of infection and complications should be admitted to hospital for assessment and care. Antibiotics should be administered within an hour of the presentation because delays are correlated with high morbidity and mortality [18]. Depending on the severity of the case, clinicians have the option between empiric antibiotic monotherapy (stable at presentation) or combined antibiotic therapy (severe sepsis, known colonization with resistant bacteria) [1,12]. Frequently used as monotherapy are β-lactam agents with anti-pseudomonal activity like: cefepime, piperacillin/tazobactam, ceftazidime, meropenem, imipenem/cilastatin. Regarding combined empiric antibiotic therapy, the guidelines recommend the use of an anti-pseudomonal agent + aminoglycoside [19]. Vancomycin intravenously may be added to IV monotherapy or combination therapy depending on the specific indication as can be seen in Table 2.

The initial choice empirical therapy must take into consideration the local epidemiological bacterial isolates and resistance changes since it may be required for coverage of MRSA or resistant Gram-negative bacteria, both in patients with low risk of complications and those with high risk [6].

Table 2 describes the management of FN patients proposed by internationals guidelines, the antibiotic regimens that are utilized according to the risk stratification score, and whether they are managed in a hospital or outpatient setting, as well as the duration of treatment and specific indication for adding vancomycin [1,6,20,21].

EVALUATION OF THERAPEUTIC RESPONSE AND LENGTH OF THERAPY IN THE CASE OF DOCUMENTED INFECTIONS

The main objective of monitoring a patient with FN is to rule out the development of new infectious foci by daily physical examinations and assessments of vital signs three times per day. Blood cultures must be performed every 48 hours in patients with persistent fever, along with a hemogram, biochemistry, daily kidney and liver function tests, and sample of any additional foci that may be present [7].

The empirical antibiotic coverage should be broadened to include resistant Gram-negative bacilli, Gram-positive bacteria, and anaerobes in patients with persistent fever (>48 h) who also have hemodynamic deterioration or clinical worsening [7]. Stable patients who continue to develop fever after receiving broad-spectrum antibiotics for more than 3 to 4 days, without an identified source, do not require extending the antibiotic spectrum [4]. If specific empiric treatment against Gram-positive bacilli (eg, glycopeptide) is initiated, it should be stopped 48 h after initiation, unless the initial suspicion is confirmed [17].

Regarding antifungal medication, this is reserved for patients with severe disease having persistent fever of unknown cause after 4 to 7 days of antibiotic therapy and who have neutropenia that is anticipated to last longer than 7 days [17,21]. If invasive fungal infection is suspected additional investigations are required: galactomannan serology and 1,3-β-D-glucan, computed tomography of the sinuses, chest/abdomen/pelvis according to symptoms. Additionally, empiric antifungal treatment should be taken into account, particularly for those getting allogeneic hematopoietic stem cell transplants, with acute leukemia or those with high doses of corticosteroids who are at a higher risk of developing mold infections [12].

The duration of treatment for patients with proven infections is decided based on the microorganism involved and the site of infection as can be seen in Table 3 [1].

CHEMOPROPHYLAXIS

Currently, both European and American guidelines recommend antimicrobial prophylaxis for patients with high risk of febrile neutropenia, defined as neutropenia lasting more than 7 days, with varying regimens for when to begin and stop treatment as well as different strength of recommendations. There are also considered to be at high risk, regardless of the length of neutropenia, patients with neutropenic fever who have chronic comorbidities or severe signs of hepatic or renal dysfunction. Given the fact that infections are more common after intensive cytotoxic chemotherapy using preventive antibacterial, antiviral, and antifungal medicines in individuals at high risk of such infections is one strategy for lowering the complications [7,22].

Antibacterial prophylaxis is suggested in high risk patients (undergoing allogeneic hematopoietic cell transplantation (HCT) and those receiving induction CHT for acute leukemia) and selected intermediate risk patients when neutropenia is expected to last between 7-10 days (patients taking a purine analog; those with lymphoma, chronic lymphocytic leukemia, or multiple myeloma; autologous HCT recipients) [23]. Fluoroquinolone (FQ) prophylaxis can be made with levofloxacin or ciprofloxacin, however before administration, the patient's benefits in terms of mortality, febrile episodes, bacteremia, as well as the risks - resistance, collateral damage, side effects must be taken into account, given the fact that FQ resistance of GN bacteria varies between 40% to 50% according to several multicenter studies [24,25].

Recent meta-analysis published showed no mortality reduction after FQ prophylaxis, but it was found the reduction of febrile neutropenia episodes

TABLE 2. Management of neutropenic fever patients according to IDSA, ESMO, NCCN, ECLID-4

	ECLID-4 (2011)	NCCN (2018)	ESMO (2016)	IDSA (2011)
Low risk patients >2	**Escalation or de-escalation approach**: *Escalation* in case of uncomplicated infection, without history of resistant bacteria infection/ colonization, center with low AMR. – antipseudomonal cephalosporin – piperacilin - tazobactam – other options: ticarcillin-clavulanate, cefoperazone-sulbactam, piperacillin + gentamicin	**Oral antibiotic therapy**: Ciprofloxacin + amoxicillin/ clavulanate, levofloxacin, moxifloxacin, ciprofloxacin + clindamycin for patients allergic to penicillin. **IV antibiotic monotherapy**: imipenem/cilastatin, meropenem, piperacillin/ tazobactam, or an extended-spectrum antipseudomonal cephalosporin-cefepime or ceftazidime	***Oral antibiotic therapy***: single agent quinolones, or quinolones + amoxicillin/ clavulanate	**Oral antibiotic therapy**: ciprofloxacin + amoxicillin- clavulanic acid, levofloxacin, or moxifloxacin or ciprofloxacin plus clindamycin **IV antibiotic therapy**: cefepime (home/ outpatient setting)
High risk patients <21	*De-escalation*: critically presentations, history of infection/colonization with resistant bacteria, centers with high AMR. -monotherapy with carbapenems -combination therapy: antipseudomonal β-lactam+ quinolone or aminoglycoside; colistin + β-lactam +/- rifampicin. Glycopeptide if risk factors for GP bacteria is present.	**IV antibiotic monotherapy** (intermediate- or high-risk patients): cefepime; imipenem/cilastatin; meropenem; piperacilin/ tazobactam; ceftazidime **IV antibiotic combination therapy:** aminoglycoside combined with an antipseudomonal agent	**Broad spectrum IV antibiotics.** **Monotherapy:** anti-pseudomonal cephalosporin like ceftazidime or cefepime, imipenem, meropenem or piperacillin– tazobactam **β-lactam antibiotic + aminoglycoside**- P. aeruginosa sepsis or in centers with known intermediate susceptibility of Gram-negative bacilli to β-lactams.	**Monotherapy** with an antipseudomonal β-lactam agent, such as cefepime, a carbapenem (meropenem or imipenem-cilastatin), or piperacillin-tazobactam. **IV antibiotic combination** in case of complications (add aminoglycoside, quinolones, and/or vancomycin)
Gram-positive coverage	Escalation, de-escalation approach: – Escalation: add vancomycin only if the patient is deteriorating – De-escalation: skin infections, catheter related infections, MRSA, VRE colonization, pneumonia, hemodynamic instability	– infections of soft tissues – clinical instability (hypotension, shock) – vascular access – BSI with GPB before identification – colonization with penicillin/ cephalosporin–resistant pneumococci or MRSA	– central IV catheters – cellulitis	– pneumonia – clinical instability – skin and soft tissue infections – central IV catheter infections
Empiric antifungal coverage	Escalation/de-escalation approaches: – consider further workup for fungal pathogens if not responding to antibiotics after 3-4 days	– necrotizing ulceration – thrush – retrosternal burning/ dysphagia – pneumonia with mold suspected – suspected sinus/nasal infection with suspicious CT/ MRI findings – fever continuing >4 days of empiric antibiotics	– not responding to antibiotics after 3-7 days – suspected fungal exposure (target mold)	– high risk patients not responding to antibiotics after 3-7 days of appropriate therapy with fever of unknown origin

	ECLID-4 (2011)	NCCN (2018)	ESMO (2016)	IDSA (2011)
Duration of empiric therapy	Clinically or microbiologically documented infection-continue for at least 7 days, or until the infection is microbiologically eradicated and the patient has been afebrile for at least 4 days. FUO – stop if patient stable for 72-96 h and afebrile for >48 h, regardless of ANC	Minimum required period for **documented infections** is **between 7-14 days**, based on type of infection. In case of **FUO** discontinued if patient afebrile and ANC>500 cells/μL and recovering or in case of ANC<500 and afebrile: – de-escalation to prophylactic antibiotics – antibiotic therapy until the neutropenia resolves	Clinically or microbiologically proven disease and FUO: ANC > 500 cells/μL and recuperating afebrile, and asymptomatic for > 48 h, or if ANC 500 cells/μL but afebrile for 5-7 days, consider discontinuation	The initial regimen should be continued in patients with unexplained fever or in those with clinically or microbiologically proven infections until *ANC>500 cells/μL, patient afebrile and asymptomatic >48h*

AMR – antimicrobial resistance, BSI – bloodstream infections, GPB – gram positive bacilli, MRSA – methicillin resistant Staphylococcus aureus, VRE – vancomycin resistant Enterococcus, ANC – absolute neutrophil count, FUO – fever of unknown origin.

TABLE 3. Length of therapy in the case of documented infections

Site of infection		Minimum duration
Skin/soft tissue		7–14 days
Bloodstream infection	Gram-negative	10-14 days
	Gram-positive	7-14 days
	S. aureus	4 weeks from first negative blood culture
	Yeast	≥2 weeks after first negative blood culture
Bacterial sinusitis		7-14 days
Bacterial pneumonia		7–14 days
Fungal (mold and yeast)	*Candida* spp.	minimum of 2 weeks after first negative blood culture
	Mold (eg, *Aspergillus*):	minimum of 12 weeks

between 10% to 13% of the patients, as well as the significant reduction of BSI [26,27,28]. Regarding which FQ to use, a meta-analysis that summarizes data over 40 years which included 113 randomized or quasi-randomized trials with 13677 cancer and HSCT patients, demonstrated that levofloxacin significantly reduces the rates of bacteremia and febrile neutropenia, but this reduction was not observed in ciprofloxacin prophylaxis [26].

For patients at high risk of *Pneumocystis jirovecii* pneumonia (CHT regimens with >3.5% risk; patients receiving treatment with prednisone equivalents greater than 20 mg/day for at least 1 month) or purine analogues, prophylaxis with TMP-SMX is recommended [3].

Antifungal prophylaxis. Patients at risk for deep, sustained neutropenia (the majority of acute myeloid leukemia/myelodysplastic syndromes (AML/MDS) or HSCT patients pose a higher risk of invasive fungal infection (IFI), primarily related to *Aspergillus* spp. and *Candida* spp. The preferred option among this patient is oral triazoles like posaconazole and voriconazole or other choices like echinocandins are available. However, posaconazole is the first line agent due to the fact that voriconazole has unpredictable metabolism and higher probabilities of adverse effects. Prophylaxis with fluconazole could be recommended for patients receiving new-generation immunomodulatory, monoclonal antibody therapy for relapsed and refractory myeloma as well as for patients undergoing CAR T-cell therapy. Subjects with solid tumors are not typically advised to receive antifungal prophylaxis (29].

Antiviral prophylaxis is recommended for all patients who are seropositive for the *herpes simplex virus* and receiving allogeneic HCT or induction chemotherapy for acute leukemia. The prophylaxis is done with acyclovir or valacyclovir. Additionally, antiviral prophylaxis is offered for HCT recipients who test positive for the *varicella-zoster virus*. Usually, antiviral prophylaxis is done until the mucositis disappears, or the white blood cell count improves. In people with severe graft-versus-host-disease (GVHD) and/or who need continuing immunosuppression, it is often maintained for one year or more, as well as in HCT recipients seropositive for VZV [23]. Regarding hepatitis B virus (HBV) reactivation or hepatitis C virus (HCV) exacerbation, patients presenting a high risk for reactivation with potential risk of acute liver failure are individuals with HBsAg +, anti-HBc antibodies, CHT regimens with monoclonal antibodies - rituximab, ofatumumab, male and old patients [30]. In patients with chronic HBV (HBsAg+) prophylaxis with a nucleoside reverse transcriptase inhibitor (entecavir or tenofovir) should begin two weeks prior to the start of therapy and continue for 12 months after the last round of treatment. Regarding patients with occult

hepatitis B virus infection (OBI) (HbsAg-negative/antiHBc-positive), prophylaxis will be administered to patients treated with high risk cancer therapies like monoclonal antibodies and in case of HCT, for 12-18 months after the end of cancer treatment [7]. Antiviral prophylaxis is not recommended in patients with solid tumors [23].

PREVENTION OF FEBRILE NEUTROPENIA: PROPHYLAXIS WITH GRANULOCYTE – COLONY STIMULATING FACTOR (G-CSF)

G-CSF prophylaxis is used to lower the risk of infection in patients with non-myeloid malignancies who are receiving myelosuppressive CHT treatment. Also, G-CSF decrease the time for neutrophil recovery and the duration of FN. According to the intensity of CHT regimen, and the risk of FN, patients are divided into 3 groups: high risk of FN (>20%), intermediate-risk group (10%–20%), or low-risk (10%). In order to reduce the risks of FN, hospitalization, and IV antibiotic use, G-CSF prophylaxis should be administered in patients with high risk of FN (>20%]. In the case of patients with low and intermediate risk, the decision to administer G-CSF must be considered taking into account the presence of other risk factors [31].

GENERAL RECOMMENDATIONS REGARDING VACCINATION OF CANCER PATIENTS

Patients with hematological malignancies present declines in their immunity status due to multiple factors, making immunization critical for infection prevention. Considering the fact that some diseases can be prevented by vaccination, those that are at risk of developing FN should receive immunizations against particular infection [7].

Inactivated vaccines can be administrated in patients with cancers, being safe and effective. They should be prescribed at least 2 weeks before the treatment initiation, however the administration during CHT is responsible for sub-optimal response and requires serological documentation. Inactivated vaccines should not be administered after HSCT for at least six months after any immunosuppressive medication has been discontinued [7,32].

Influenza vaccine should be administered annually, given the fact that mortality in patients with cancer can reach 9-10% [7].

Another vaccine which is strongly advised in patients with cancers receiving CHT is pneumococcal vaccination, taking into account the high prevalence of invasive pneumococcal disease (IPD). According to the *Advisory Committee on Immunization Practices (ACIP)* anti-pneumococcal vaccination in patients with immunodeficiencies (congenital or acquired asplenia, sickle cell disease or other hemoglobinopathies, generalized malignancy, Hodgkin disease, leukemia, lymphoma, multiple myeloma, etc) should be made with PCV20 or PCV15 followed by PPSV23 at distance of ≥1 year. Human papillomavirus vaccination is advised for people under the age of 26 and may also be considered for those between the ages of 26 and 45 [33].

Live vaccines (varicella, MMR, yellow fever) are contraindicated in immunosuppressed patients, especially during CHT, or during immunomodulatory medication or monoclonal antibody-based maintenance therapy. After HSCT, live attenuated vaccines can be administered after a period of >24 months if patient is negative for GVHD and seronegative for respective disease [7].

MACHINE LEARNING (ML) FOR PREDICTIONS IN FN

In the last years numerous artificial intelligence programs analyse clinical data from FN patients, trying to predict which patients will develop FN or will have infections with multidrug resistant Gram-negative bacteria (MDR-GNB) [34,35]. At this point have been developed several algorithm using ML which quantify the risk of severe and febrile neutropenia in CHT patients. H. Wiberg et al. proved that their model, OFS20 has an out-of-sample AUC of 0.865 which is higher than model proposed by Lyman et al (out-of-sample AUC of 0.81) [36]. Regarding MDR-GNB predictions, C. Garcia- Vidal et al. used ML algorithms to assess the risk factors for this type of infections and determine which patients will require broad antibiotic treatment. They found a good predictive accuracy of ML algorithms, but not optimal yet, more data being necessary.

Machine learning models were also used by *L. Xiang et al.* for early detection of septic shock in kids with hematological cancers associated with fever or neutropenia. In this study they concluded that SSEW *(septic shock early warning model)*, is an artificial intelligence (AI) model superior to qSOFA score and may help physicians in anticipating the likelihood of septic shock in individuals with fever or neutropenia 24 hours before occurring [37].

CONCLUSIONS

Febrile neutropenia is a major public health problem due to the increasing number of people with cancers, being responsible for high mortality and morbidity.

The management of the febrile neutropenic patient remains a challenge for both the clinician and the patient. Although significant improvement was made regarding the management and the prevention of infectious diseases, they remain a contribu-

tory factor of increased mortality and morbidity among onco-hematological patients, caring a mortality rate up to 11% and up to 50% in septic shock.

Considering the increased rate of complications that may appear, early diagnosis and hospitalization of patients at risk, as well as initiation of empiric antibiotic therapy in the first hour are mandatory. The initial antibiotic empiric therapy should take into account the local resistance profile and the individual's healthcare history and symptoms, which may indicate the presence of resistant microorganisms. The prophylactic use of antibiotics, antifungals and antivirals is recommended for patients at risk of developing severe infections after intensive cytotoxic CHT.

In conclusion, infections are still a major issue in patients with cancer, but some of them are preventable through vaccination or prophylaxis, and thus, these measures represent a cornerstone of cancer patients' management.

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