Research Paper

Management of Febrile Neutropenia due to Chemotherapy in Latin America: An Evidence-Based Study and Expert Consensus

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Febrile neutropenia is a common and serious complication of cancer chemotherapy. This pathology is characterized by a diminished absolute neutrophil count and elevated temperature. Despite recent therapeutic advances, febrile neutropenia is still a major cause of morbidity and mortality among cancer patients in Latin America and worldwide. This onco-hematological emergency condition also involves a high risk of complications and healthcare costs. The objective of this protocol was to develop a reference tool for the evaluation and management of febrile neutropenia in a fourth-level cancer hospital in Ecuador and provide a guideline for a timely and adequate care of cancer patients. The present project implemented an extensive bibliographic search of the last 15 y which included guidelines and scientific publications. The appraisal of guidelines for research and evaluation II and grading of recommendations, assessment, development and evaluation instruments were used to develop an expert consensus and evaluate the level of evidence of each recommendation. This document compiles updated information available on the definition, risk factors, evaluation methods, treatment and special situations in cancer patients with febrile neutropenia. Moreover, the following report allows to classify patients according to their risk level and to provide the best pharmacological strategy with their respective doses and routes of administration. Cytotoxic chemotherapy often induces febrile neutropenia and may lead to serious complications including mortality. Therefore, information available on febrile neutropenia was compiled to create a comprehensive protocol of the complication.

Key words: Chemotherapy induced-febrile neutropenia, absolute neutrophil count, expert opinion, evidence-based medicine

Febrile Neutropenia (FN) is a common complication of chemotherapy and a main cause of morbidity and mortality in cancer patients[1]. Currently, FN is described as a single measurement of oral temperature≥38.3° or fever (≥38.0°) held for more than an hour. Additionally, FN is determined by an Absolute Neutrophil Count (ANC)<1000 cells/mm^3 or an expected decrease of the ANC below 500 cells/mm^3 in the following 48 h[2,3]. Severe FN is established when ANC is below 500 cells/mm^3, while deep and prolonged FN is defined by an ANC<100 cells/mm^3 for 7 or more days. This classification allows patients to be categorized into risk groups for their management[3].

The European Society for Medical Oncology (ESMO, 2016) reported an incidence of approximately 8 cases of FN per 1000 patients who received chemotherapy[1]. Despite advances in treatment of FN, the incidence of complications can reach 30.9 %[4]. Furthermore, the mortality rate of FN achieves 11 % and can increase to 50 % in case of severe sepsis or septic shock[5,6].

Unfortunately, there are limited data on the incidence and prevalence of FN in Latin America and Ecuador in particular. A multicenter study in Argentina reported 515 episodes of FN in 346 patients, of which 77 % were secondary to chemotherapy. The study group included 56.5 % of patients with hematological malignancies and 20.2 % with solid neoplasms[7].

Several risk factors can lead to the development of

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FN in cancer patients, the most representative were listed in the clinical practice guideline developed by the American Society of Clinical Oncology along with the Infectious Diseases Society of America (ASCO/IDSA). These risk factors included age≥65 y, an Eastern Cooperative Oncology Group (ECOG) score of performance status≥2, previous FN episode and associated comorbidities[3].

The risk of mortality (high/low) and complications should be classified based on prognostic indexes for an appropriate FN treatment. The Multinational Association for Supportive Care in Cancer (MASCC) score is a prognostic index used for hematological neoplasms, while the Clinical Index of Stable Febrile Neutropenia (CISNE) score is the best suited for solid neoplasms[8,9].

In case of FN with severe sepsis and septic shock, an early establishment of treatment (in less than 1 h) allows to reduce morbidity and mortality[10]. Patient care is important to consider the broad-spectrum antibiotics use, for common pathogens based on local epidemiology. On the other hand, patients can be monitored in outpatient or inpatient settings depending on individual risk factors[1,11].

In Latin American countries, no formal guidelines are currently available to direct the management of FN. The implementation of a protocol for patients with FN is crucial because it is a life-threatening onco-hematological emergency condition that involves a high risk of complications and healthcare expenditure. Therefore, the objective of this article was to develop a reference tool for the evaluation and management of FN, considering the current scientific evidence.

MATERIALS AND METHODS

Experts in clinical oncology and medical internists contributed to create a template protocol for the management of FN. An extensive literature search in English and Spanish of the last 15 y (2006-2020) was conducted. The keywords implemented in the search project were "febrile neutropenia", "risk stratification", "guideline" and "treatment". The scientific evidence was collected through PubMed search engine. In addition, updated international FN clinical practice guidelines were appropriately evaluated. In the area of drug evaluation, all available evidence from the European Medicines Agency (EMA) was included.

An online questionnaire was developed in accordance with the Appraisal of Guidelines for Research and Evaluation II (AGREE II) to reach a consensus. Consensus was defined as more than 70 % of the panel's approval. The AGREE II tool was used to assess the process of developing the document and the quality of information. It consisted of 23 items grouped into 6 domains, which included the scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability and editorial independence. Each item was rated using a seven-point Likert scale, from strongly disagree (one) to strongly agree (seven)[12]. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system was employed to assess the level of evidence for each recommendation[13]. The article did not require ethical committee approval.

RESULTS AND DISCUSSION

FN is amongst the most common complication of cancer treatment that occurs in the Nadir (lowest point) period after receiving chemotherapy[14]. This period predisposes to infections due to decreased activity of innate immunity and defense barriers as mucous membranes. Additionally, the inflammatory response to infections is altered, thus clinical assessment becomes challenging and fever is one of the few useful signs in FN diagnosis[15].

Important tests as imaging, microbiological cultures and serological and molecular examinations allow to identify the origin of infection[16,17]. However, most of the time before identifying the source of infection, is necessary to initiate an empirical treatment considering the epidemiologic variation due to the growing antimicrobial resistance[11,18]. In brief, all these aspects make the evaluation and treatment of FN challenging for healthcare institutions.

This document compiles updated information available on the definition, risk factors, evaluation methods, treatment and special situations in cancer patients with FN. The recommendations were given considering the reality of the population of a fourth-level cancer hospital in Ecuador.

Initial patient evaluation was carried out. Risk factors evaluation is essential to predict the outcome of patients with FN. These factors are divided into patient-related (advanced age, nutritional status, previous episode of FN, comorbidities) and those related to the type of underlying neoplasm (stage, remission status, response to treatment) and cancer treatment (cytotoxic regime, dose intensity, degree and duration of oral and/or gastrointestinal mucositis, severity and duration of

cytopenia)[3]. The initial evaluation sought to detect the source of active or latent reactivated infection in cancer patients who received potentially immunosuppressive treatment (Table 1)[15,19].

Classification of patients with FN was shown here. FN is a medical emergency with risk of serious infectious complications. Therefore, the use of risk stratification indexes is helpful after the diagnosis. Scales become important to decide the treatment that should be applied in outpatient or inpatient settings[9,20].

The CISNE is used to predict major complications in patients with solid tumors and seemingly stable episodes of FN (Table 2)[9].

In hematological malignancies, the MASCC score is used to identify patients with low risk of complications. In addition, MASCC helps to determine the most convenient therapeutic strategies in each case (Table 3)[20].

Low-risk patients are characterized as follows. They have no recorded fever during hospitalization, compensated comorbidities, neutropenia for less than 7 d, ECOG score 0 to 1, absence of hepatic or renal failure, MASCC>21 (hematological tumors) or CISNE≤2 (solid tumors)[11].

Low-risk patients can be managed in ambulatory settings, bearing in mind the risk factors[21]. In addition, initiation of antibiotic therapy should be performed within 60 min of the patient's arrival at the emergency service after taking culture samples[22]. Outpatient treatment is considered as acceptable if the patients have adequate oral intake, without infection or acute leukemia. Also, the patient can be managed for ambulatory depending on the doctor's decision and the access to the medical center[21,23].

The oral antibiotic regime should cover Gram-negative, Gram-positive bacteria and *Pseudomonas* (Table 4)[22-27]. In addition, after the administration of the first dose of antibiotic, the oral tolerance should be assessed and a 4 h observation period has to be maintained[12]. In patients allergic to penicillin, a good antibiotic option is clindamycin plus fluoroquinolone[2]. In addition, after 72 h, patient control should be done with a medical and laboratory assessment of urea and creatinine and with

TABLE 1: PARAMETERS TO CONSIDER IN THE INITIAL EVALUATION

Area	System/parameter	Criteria to be evaluated
Detailed history*	Drugs	Administered chemotherapy (high-risk cytotoxic drugs such as anthracyclines, cisplatin, ifosfamide, cyclophosphamide, etoposide and cytarabine)
		Chronic use of corticosteroids
		Previous antimicrobial prophylactic treatment
	Personal history	Recent surgeries
		Allergies
Physical exam*	Vital signs	Oral temperature[ł]
	Skin and mucous membranes	Degree of dehydration, integrity, presence of catheters
	Respiratory system	Signs of pneumonia
	Gastrointestinal system	Pain and peritonism
	Perianal, perineal and genitourinary region	Abscesses, presence of erythema, pain on palpation, hemorrhoids, genitourinary secretions. Rectal examination is contraindicated
	Central nervous system	Neurological status, meningeal signs, level of consciousness
Complementary exams*	Complete blood count	Erythrocytes, leukocytes, thrombocytes
	Renal function	Electrolytes, urea, creatinine
	Liver function	ALT, AST, ALP, GGT, INR, bilirubin, albumin
	Inflammatory markers	C-reactive protein, procalcitonin
	Bacteriology**	Blood culture, molecular diagnostic tests (fluorescence *in situ* hybridization using peptide nucleic acid probes for Gram-positive and Gram-negative bacteria, mass spectrometry, *Clostridium difficile*)
	Virology**	Respiratory and gastrointestinal molecular diagnostic panels
	Mycology**	Fungal culture, beta (ß)-D-glucans, *Aspergillus* galactomannan immunoassay, molecular diagnostic methods (fluorescence *in situ* hybridization using yeast peptide nucleic acid probes)
	Image*	Depends on the site of origin of the infection, chest x-ray

Note: ALP: Alkaline Phosphatase; ALT: Alanine Transaminase; AST: Aspartate Transaminase; GGT: Gamma-Glutamyl Transferase; INR: International Normalized Ratio; [ł]Avoid axillary temperature, rectal temperature is contraindicated; *Klastersky *et al*. Management of febrile neutropaenia (2016)[1]; **Babady *et al*. Laboratory diagnosis of infections in cancer patients (2016)[19]

TABLE 2: RESULTS OF CISNE SCORE

Characteristics	Points
ECOG PS≥2	2
SIH*	2
COPD	1
Chronic cardiovascular disease	1
Mucositis NCI grade≥2	1
Monocytes<200 per µl	1

Note: CISNE score: 0 low risk, 1-2 intermediate risk, ≥3 high risk; CISNE: Clinical Index of Stable Febrile Neutropenia; COPD: Chronic Obstructive Pulmonary Disease; ECOG PS: Eastern Cooperative Oncology Group Performance Status; NCI: National Cancer Institute and SIH: Stress-Induced Hyperglycemia; µl: microliters; *Glucose≥121 mg/dl or ≥250 mg/m^2 in diabetic patients (or in patients receiving corticosteroids)[9]

TABLE 3: RESULTS OF MASCC INDEX

Characteristics	Weight
Burden of illness	
Without or mild symptoms	5
Moderate symptoms	3
Without SBP hypotension (<90 mmHg)	5
Without active COPD, chronic bronchitis, emphysema, decreased FEV, need for oxygen therapy, corticosteroids or bronchodilators administration	4
Solid tumor or without previous fungal infection	4
Without dehydration	3
Outpatient status at fever onset	3
Age less than 60 y	2

Note: MASCC score: ≤21 high risk, >21 at risk; COPD: Chronic Obstructive Pulmonary Disease; FEV: Forced Expiratory Volume; MASCC: Multinational Association of Supportive Care in Cancer; mmHg: millimeter of mercury and SBP: Systolic Blood Pressure[20]

TABLE 4: ANTIBIOTICS RECOMMENDED FOR LOW AND HIGH-RISK PATIENTS

Risk classification	Recommendation	Level of evidence*	Expert consensus**
Low risk	Ciprofloxacin 750 mg orally BID plus amoxicillin-clavulanic acid 1 g P.O. QD***[22]	I, A	The use of these antibiotics is recommended because they are safe and effective [I, A]
	Levofloxacin 500-750 mg P.O. QD[24]	II, B	The use of fluoroquinolones is not recommended in our setting due to high rates of resistance [I, B]
	Moxifloxacin 400 mg P.O. QD[25]	I, B	The use of fluoroquinolones is not recommended in our setting due to high rates of resistance [I, B]
High risk	Piperacillin tazobactam 4,5 g I.V. QID[26]	I, A	Comparison by meta-analysis found comparable efficacy between monotherapy (e.g., anti-pseudomonal cephalosporins cefepime or ceftazidime, piperacillin-tazobactam or meropenem, imipenem) and combination therapy [I, A]
	Cefepime 2 g I.V. TID[26]	I, A	
	Imipenem 500 mg I.V. QID[26]	I, A	

Note: BID: Every 12 h; I.V.: Intravenous; mg: milligram; P.O.: Oral administration; QID: Every 6 h; QD: Every day; TID: Every 8 h; g: gram; *Level of evidence: Grade was used; **Expert consensus: Conducted by guideline authors[1,25-27]

tests to evaluate the bone marrow[1].

In patients with ANC>500 cells/mm^3, treatment can be discontinued if fever is overcoming and cultures are negative. In contrast, if the patient has an ANC<500 cells/mm^3, treatment can be discontinued, in case if there are no associated complications and no fever for up to 5-7 d[1].

Low-risk patients should be hospitalized if they are confirmed with the infection in the cultures and physical examination and have oral intolerance. Furthermore, inpatient treatment is recommended when there is difficult to implement an adequate outpatient follow-up. In these patients the treatment will be same until they were classified as high-risk[23].

A high-risk patient meets at least one of the following criteria-MASCC score<21 and CISNE≥3, neutropenia for more than 7 d, fever and decompensated comorbidities. Other important criteria are elevation of transaminases (>5 times normal), renal failure, altered state of consciousness, suspected infection of the central nervous system and hydro electrolyte imbalance[2,22].

High-risk patients should be hospitalized and the initial empirical antibiotic treatment within the first 60 min of their evaluation must be implemented[22]. Antibiotic selection is an important area to take into account as well as local epidemiology and grades of resistance for an appropriate treatment[24].

According to international guidelines such as National Comprehensive Cancer Network (NCCN) and ESMO, for the treatment of high-risk patients the use of at least one beta-lactam anti-pseudomonal drug is recommended (Table 4)[1,11].

Even though standard treatment with broad-spectrum antibiotics is available, there are several circumstances in the clinical practice that require a specific regime. In these cases, treatment duration can vary and local antibacterial guidelines must be followed (Table 5)[1].

Sepsis in FN is shown here. Patients developing sepsis

TABLE 5: SPECIFIC INDICATIONS FOR ALTERNATIVE THERAPIES

Focus of infection	Treatment and evidence level
Central venous catheter	A glycopeptide such as vancomycin should be administered to cover Gram-positive organisms [III, A]
Pneumonia	Antibiotic coverage should be extended to treat atypical organisms, such as *Legionella* and *Mycoplasma* by adding a macrolide or a fluoroquinolone to a beta-lactam antibiotics [V, D]
Pulmonary infiltrates	Treatment for suspected aspergillosis (in case of CT infiltrates) could consist of voriconazole or liposomal amphotericin B [I, A]
	These antifungals can be combined with an echinocandin in non-responsive disease [IV, B]
	High dose cotrimoxazole is the treatment of choice for suspected Pneumocystis infection [I, A]
Vesicular lesions/ suspected viral infection	After appropriate sampling, acyclovir therapy should be initiated [I, A]. Ganciclovir (or foscarnet) should be substituted only when there is high suspicion of cytomegalovirus invasive infection [I, A]
Suspected meningitis or encephalitis	Bacterial meningitis should be treated with ceftazidime plus ampicillin (to cover *Listeria monocytogenes*) or meropenem [II, A]
Cellulitis	The addition of vancomycin expands coverage against skin pathogens [V, D]
Intra-abdominal or pelvic sepsis	Start with metronidazole [V, D]
Diarrhea	A screening for *Clostridium difficile* is necessary and if suspected, oral treatment with vancomycin or metronidazole should be administered [V, D]
Candidiasis	Starting of antifungal therapy is recommended in patients whose fever does not respond with broad-spectrum antibiotics after 3-7 d of appropriate treatment [I, A]
	Liposomal amphotericin B and an echinocandin antifungal such as caspofungin are appropriate first-line treatments if the patient has already been exposed to an azole antifungal or if it is known that the patient is colonized by non-albicans *Candida* [I, A]

Note: CT: Computed Tomography. The recommendations were written exactly as the original source[1]

TABLE 6: SEPSIS CRITERIA IN PATIENTS WITH FN

S. No	Criteria
1	Hypotension with mean arterial pressure<65 mmHg*
2	Serum lactate>2 mmol/l*
3	Urinary output≤0.5 ml/kg/h for more than 2 h (30 to 50 ml/Kg)*
4	Arterial hypoxemia PaO_2-FIO_2<300 mmHg
5	Respiratory rate>22 breaths/min
6	Creatinine>2 mg/dl or increase>0.5 mg/dl
7	Total bilirubin>4 mg/dl
8	Platelet count<100 000/µl secondary to infection
9	INR>1.5

Note: dl: deciliter; FiO_2: Fraction of inspired Oxygen; h: hour; INR: International Normalized Ratio; kg: kilograms; mg: milligrams; ml: milliliters; mmHg: millimeters of mercury; mmol/l: millimoles per liter; PaO_2: Partial pressure of Oxygen; µl: microliter and *For a patient who is not responding to crystalloid resuscitation[10,28,29]

due to FN should get a priority evaluation by intensive care unit when presenting one of the following criteria (Table 6)[10,28,29].

Routine use of Granulocyte Colony-Stimulating Factor (G-CSF) in patients with FN is not recommended because no effect on overall mortality was detected[30]. However, G-CSF can reduce hospital stay and improve patient's ability to recover neutrophil count. Moreover, it was observed that patients who received G-CSF had a shorter duration of neutropenia, faster recovery of fever and a shorter duration of antibiotics use[31]. The use of G-CSF is recommended in patients with high risk of complications or poor prognostic factors. These factors include prolonged or profound neutropenia, age>65 y, pneumonia or other documented infections, sepsis and invasive fungal infection[30]. G-CSF administration should be maintained in patients who received it prophylactically at FN diagnosis time[11].

The present document was intended to be used as a guide for diagnosis and treatment of FN in oncologic care institutions. An extensive literature search was performed and international published expert experience was considered, given that currently no FN clinical practice guidelines for diagnostic and treatment of the oncologic population exist for Latin American countries.

The present protocol established the risk categorization criteria for FN patients according to age, functional status, history of neutropenia and comorbidities. In addition, concerning treatment, FN patients were classified in low and high-risk categories applying CISNE and MASCC prognostic scores, since they are the most used and appropriate tools implemented for this evaluation. The therapeutic approach relied on the risk categorization and on the international epidemiology of microorganisms. The protocol yielded a practical document with recommendations for the management of adult cancer patients with FN due to chemotherapy, seeking objectivity and clinical implications.

When compared to the ESMO FN management reference guidelines (2016 Clinical Practice Guidelines), this document followed the same organization except for data concerning the most frequent microorganisms, antibiotics and G-CSF prophylaxis used. Furthermore, it did not consider the application of algorithms management, since not all institutions in Ecuador have access to the same supplies and drugs. On the other hand, the document had similar recommendations on risk stratification and treatment options for low and high-risk patients underscored with ESMO guidelines[1].

In comparison to NCCN Prevention and Treatment of Cancer-Related Infections Guideline (2020), the present work did include a section on prevention and prophylaxis of FN. As for NCCN guidelines, it considered the use of G-CSF in patients with persistent fever, bacteremia or clinical deterioration. While the United States (US) guidelines expanded options for subsequent treatment with drug doses, e.g., antifungal or antiviral agents, the document was comparable with respect to the use of the sequence of initial assessment and categorization into low and high-risk patients examining individual factors and scores. Moreover, the recommended treatment was similar, considering local microbiology patterns and the specific site of infection[11].

In patients with septic shock and high-risk FN, the most frequently identified germs were Multidrug-Resistant (MDR) and according to this article, the use of broad-spectrum antibiotics such as piperacillin tazobactam or meropenem are recommended as empirical treatment[32].

Other limiting points to consider in our oncologic population with FN concern the delay of access to emergency rooms, technical and logistic problems, and limited laboratory availability. Likewise, the unfamiliarity of physicians with the management of FN can have a negative impact due to the delay of antibiotic therapy initiation for up to 3 h. Nevertheless, according to the literature, this delay in the antibiotic administration of antibiotics does not affect the patient's stay of hospitalization or admission in the intensive care unit[33].

The optimal duration of antibiotic treatment in patients with FN is not fully elucidated. According to the ANTIBIOSTOP study (2018) that included 123 patients with 238 cases of neutropenia, early discontinuation of antibiotics was safe in a FN patients; the same recommendation was reported by the European conference on infections in leukemia[34].

The superiority of prolonged antibiotic administration in patients with FN and documented infections, especially pneumonia, was demonstrated in Ram *et al*. randomized study[35].

Currently, one of the complications to be considered in cancer patients with FN is the infection with Severe Acute Respiratory Syndrome Coronavirus type 2 (SARS-CoV2). At the moment, MASCC score has not been validated in patients with suspected or confirmed SARS-CoV2 infection. Although it sounds reasonable to expect that the score will be useful in this setting, the MASCC score should be validated in this group of patients to allow a development of new models of care[36].

One constraint to be mentioned in writing the document was the absence of regional epidemiological data focused on FN causing microorganisms. Due to this limitation, the recommended therapies were directed towards MDR germs, which lead to empirical use of broad-spectrum drugs. The implementation of more regional studies should be highly recommended to detect the most frequent microorganisms in FN patients in Latin American countries. Another constraint affecting low-risk FN patients is the lack of follow-up to outpatient antibiotic treatment due to limited resources. In this group of patients, empirical oral antibiotics could be used as an alternative treatment, as previously described, due to the low expected risk of mortality.

In conclusion, FN is a common complication in oncologic patients receiving chemotherapy. Guidelines and protocols are essential to define the optimal management according to the reality of each region. Therefore, the present protocol was developed to guide the treatment of patients with FN in an oncologic hospital, emphasizing the fact that treatment should always be individualized according to the risk categorization of each patient. Additional data on FN will be needed in the future for an appropriate management of the complication and to improve its outcome in cancer patient populations.

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