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RESEARCH ARTICLE

FEVER AND NEUTROPENIA IN THE PEDIATRIC PATIENT, A DIFFERENT PERSPECTIVE BETWEEN LATIN AMERICA AND EUROPE

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ABSTRACT

Introduction: In Mexico, according to the latest data from the Ministry of Health, there are between 5,000 and 6,000 new cases of cancer in children under 18 years of age, with leukaemias in more than 50%, with an approximate survival of 56% at the time of diagnosis, however in developed countries can reach up to 90%. Mexico has an annual average of 2,150 deaths from childhood cancer in the last decade according to figures from the Statistical Epidemiological System of Deaths (SEED). The main complications of these patients are when they present infectious processes, chemotherapy and immunosuppression presented throughout their treatment make them high points for research, new topics and proposals in the treatment during the last years have made the Medical advances change the prognosis and increase the survival. Many acute phase reactants have been studied as part of the initial approach and follow-up of patients during the process of neutropenia and fever, so much so that they have been included in global assessment scales as predictive factors to the response to treatment. Starting with studies such as the one presented below is of the utmost importance to justify the priority in their approach. Another problem found in these patients is when choosing which antibiotic is the best, multidrug resistance secondary to the indiscriminate use of antibiotics have recently caused problems, that is why we have had to continue investigating which are the main etiological agents found at the Naval Medical Center to be able to propose antibiotic treatments reducing this problem. **Objective:** We present a review article where we will observe the main mechanism by which treating these patients is so important. Information for first contact physicians; who receive these patients in an emergency service and in many cases do not know how to approach them. Always leave in the patient is immunocompromised and that the hours are important so that the delay of the treatment is an important point for the survival of the same. **Conclusion:** Fever and neutropenia (FN) in pediatric patients has been a problem in recent years, perhaps a world which many are unaware of, it is always important to start with the patient being in an immunosuppressed state and we as a physician having a broad vision What are the etiological agents involved in these cases will result in the importance of knowing how to treat them. Sometimes it is important to start from a simple antibiotic scheme, but we must take into account that the epidemiology is different between a hospital center and another.

INTRODUCTION

Cancer patients tend to present immunocompromised data either secondary to their underlying pathology or due to the chemotherapeutic treatment used. Neutropenic patients with a febrile process is the main scenario of an infectious process of either bacterial, viral or fungal etiology; the first being the most frequent of these (Paganini *et al.,* 2011). Other risk factors to consider in these patients are the presence of mucositis, central venous catheter, days of in-hospital stay, use of steroids, among others (Bailey *et al.,* 2009). Approximately 30-60% of patients with hemato-oncological diseases have a febrile process; with a mortality of up to 12% (Averbuch *et al.,* 2013), accompanied by up to 83.5% of cases of neutropenia (Kuo *et al.,* 2015). During the eighties, a predominance of gram-negative bacilli was reported, followed by a decrease in the frequency of these pathogens and a relative increase in Gram-positive cocci, which currently have an incidence between 45 and 70% (Bailey *et al.,* 2009), studies in Europe have found that up to 87 different pathogens can be identified, where 65% were Gram positive bacteria and 29% Gram negative, without finding clinical difference between the duration of fever, time of hospitalization or the need for care in a Pediatric Intensive Care Unit (Agyeman *et al.,* 2014). In Latin America there are few records on these complications in cancer patients, in Chile, data from the National Children's Antineoplastic Drug Program (PINDA) estimate an incidence of 12 to 14 cases per 100,000 (Paganini and Santolaya, 2011). Finding reports that, in some cases, bronchopneumonia in 81.8% of the cases and mucositis between 15 and 35% as the main clinical manifestations. Multiple infections in patients with leukemia or lymphoma are polymicrobial between 5% and 60% (Bailey *et al.,* 2009). Studies carried out by the University of Taiwan report that in 23.8% of the patients the blood cultures performed during a period of neutropenia and fever were positive for Gram-positive bacteria, the most frequent being Steptococcusssp in 7.1% Enterococus 2.4% and

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Staphylococcus aureus in a 3.2% Gram-negative bacteria found that the most isolated organisms corresponded to Escherichia coli in 22.2% and Klebsiellapneumoniae in 13.5% and Pseudomonas aeruginosa in 7.9% (Kuo *et al.,* 2015). The approach of a patient with fever of unknown origin is different in pediatric patients without relevant antecedents, than in those oncological. However, it has been found that even in healthy patients in 84.9% the cause of the fever was identified, being the most common cause an infectious process in 37.6%, followed by malignant processes in 17.2% (Gonzalez *et al.,* 2015). In cancer patients, fever may also be the first manifestation of an infection, especially during periods of neutropenia (Chen *et al.,* 2015). Although it is true that the recommendations in various guidelines regarding antibiotic management should be initiated as soon as possible, up to one hour after the onset of symptoms, these recommendations are based on the guidelines of surviving sepsis, however other studies such as the one carried out by Verónica De la Maza and collaborators in 2015, where only 25% of cancer patients receive antibiotic treatment before 60 minutes with an average dose of antibiotics between 60-246 minutes after onset of fever; no significant variation was found between the time of administration of antibiotics or the increase in days of hospitalization and the appearance of sepsis (De la Maza *et al.,* 2015).

Another problem that has arisen lately has been the follow-up that has been given to them during the presentation of the febrile symptoms; taking into account various scales, clinical manifestations and biochemical alterations both at the time of diagnosis and subsequently. One of the most important advances is the emergence of acute phase reactants, where in many tertiary hospitals in Latin America, are the levels of procalcitonin with which health personnel help in the follow-up of these patients before a bacterial picture; However, the lack of economic resources in many cases makes this impossible. It must be considered that procalcitonone has the advantage that elevation of up to 500 times in the first 2-4 hours after infection (Reyna *et al.,* 2015) could be an indicator of severity; having as a cohort point values greater than 2ng / dL (10); but studies have been found where values of up to 0.2ng/dL could already indicate the perfect scenario of a feverish process. Among other reactants that could be found C-reactive protein, which has also been controversial, because although it has been widely described that this has a lower sensitivity and specificity; in many cases, it has helped decision-making in certain hospitals, with the disadvantage that it may present a significant elevation in asymptomatic patients; like the studies carried out in 2016 by Sugiura and collaborators; comparing that its elevation without the presence of symptoms of inflammatory response in patients even presented a picture of neutropenia and fever in 55.6% of the cases. Being this as a reason to start treatment prophylactically; since upon initiation of antibiotic treatment, only 6.75 of the patients presented with neutropenia and fever compared to 31% who did not receive antibiotic treatment (Sugiura *et al.,* 2016).

Although the diagnosis of cancer is lower in pediatric patients compared to adults, in the United States approximately 1 in 285 children will have a diagnosis of cancer before the age of 20 (Castagnola *et al.,* 2007); presenting between 0.5 and 3% of all malignant neoplasms in the world. In general, cancer of hematological origin is the main cause of pediatric cancer up to 40%, with leukemia being the most frequent of these in 30% (Cancer in children and adolescentes, 2014), followed by malignant tumors of the central nervous system in 18% and lymphomas by 14% (12). By 2016, 10,380 new cases of cancer in children between one and fourteen years of age are estimated in the United States, and 1,250 cancer deaths per year are expected; finding a reduction in mortality of up to 70% compared to previous years (Cancer in children and adolescentes, 2014). In Mexico there is little information on the frequency of neoplasms in the states, according to the National Health Survey (ENSANUT) of 2012 a total of 10 021 929 children between 0 and 4 years old live in the country, and 11 469 013 among the 5 and 9 years (Hutter, 2010) had some oncological condition; however, the most recent data on cancer incidence according to the Clinical Practice Guidelines are from 2005, where a total of 130 new cases per million were estimated, representing a total of 4160 cases of cancer per year and acute leukemia. between 1000 and 1200 new cases per year (Encuesta nacional de salud y nutrición, 2012).

The presence of immunosuppression in the oncological patient during antineoplastic treatment represents a risk factor for the presence of infectious events, changes in the innate and adaptive system that favor the invasion by diverse microorganisms. At the level of the innate system, the cutaneous barrier is broken with the use of catheters, and blood samples are taken repetitively, as well as inflammation and mucosal injury due to chemotherapy, which facilitates the invasion of pathogens. Additionally, one of the main effects is the compromise at the level of neutrophils, circulating monocytes and tissue macrophages, where cytotoxic agents cause alterations in chemotaxis, in the bactericidal function, in the production of superoxide agents; thus causing a decrease in the number of neutrophils and monocytes (Chen *et al.,* 2015). In the patient with cancer; the specialist doctor should not only consider the treatment for the neoplasm but also the management of the complications in which the infections are the main cause of morbi-mortality in these patients due to the state of inherent immunosuppression. Fever being the first manifestation (Naurosis *et al.,* 2010) of an infection in most cases, especially during a process of neutropenia. Episodes of fever occur in approximately one third of neutropenic patients; either induced by chemotherapy or subsequent to it (De la Maza *et al.,* 2015). Despite advances in the prevention and treatment of patients with neutropenia and fever, it remains one of the most common complications in these patients, where mortality is between 5% in patients with solid tumors and 11% in patients with hematologic tumors. Those with a Gram-negative bacteremia were 18% worse than Gram-positive bacteremia in 5% (Naurosis *et al.,* 2010). Febrile neutropenia (NF) constitutes a frequent complication and an infectious emergency, during the treatment of leukemia; that for 2 years of treatment of leukemia reach up to 6 frames in average febrile neutropenia (Paganini and Santolaya, 2011; De la Maza *et al.,* 2015). This is the second cause of hospital admission in pediatric oncology after admissions for chemotherapy, prolonging the hospital stay up to approximately 13 days (Chen *et al.,* 2015). As already mentioned before; During the cytotoxic treatment in oncological patients the probability of presenting a process of febrile neutropenia increases, that is why to understand the pathology of an infectious process in these patients one must first understand the immunological changes that come to present. The first line of defense in the body is the innate immune response; which includes specialized cells of the various apparatus and systems of the body, from the respiratory tract to the genitourinary.

The oncological patients come to present changes in these barriers by two mechanisms mainly:

- Local invasion of various solid tumors in certain membranes and tissues, which after treatment, whether surgical or radiotherapy, have a lesion in said tissues.
- The use of various catheters and means of peripheral and central access for the treatment of cancer and its complications being these are an entry measure for various microorganisms (Paige, 2013).

As previously mentioned; the next change is more related to changes in the second line of defense of innate immunity; such as phagocytes, neutrophils, monocytes and macrophages. Neutropenia is usually defined as the presence of absolute neutrophils less than 1500 cells/mm (Newberg and Dale, 2013), and the severity of complications may depend on the absolute number of neutrophils. However, in patients with a history of cancer, they have a certain predisposition to present low absolute values of neutrophils; that is why, in this type of patients, neutropenia could be considered as those with a value below 500 cel. Absolute neutrophils/mm (Freifeld *et al.,* 2011) or when a fall is predicted to a figure <500 cel./mm in the next 24 to 48 hours (Paganini and Santolaya, 2011). Other guidelines allow to classify the severity of neutropenia according to the absolute value of cells, considering neutropenia (Paganini and Santolaya, 2011; Chen *et al.,* 2015):

• Mild: 1500-1000 cells / mm
• Moderate: 1000-500 cells / mm
• Severe: <500 cells / mm

However, it is better to handle the last concept that is applied in the Latin American guides. Regarding the definition of Fever, it has been found that there is no difference between different guides; considering it as a single record of axillary temperature greater than 38.5ºC or greater or 38ºC with a separation, between both determinations, of at least one hour (Paganini and Santolaya, 2011; Agyeman *et al.,* 2014; Gonzalez Galviz *et al.,* 2015). Once these concepts have been reviewed, it is important to highlight the role of neutrophils in the face of infection or bacteremia as part of the innate immune response. The innate immune response has its beginning from the recognition of microorganisms through structures known as molecular patterns associated with pathogens, such as lipopeptides, liposaccharides, nucleic acids; among others; These are recognized by cellular receptors that subsequently intervene in the release of certain proinflammatory cytokines such as IL-6 IL-8 and IFN-gamma. As already mentioned, the first line of defense against various infections are the barriers of the skin and mucous membranes in the body, which through the action of the antigen presenters; mainly in the dendritic cells, there is an activation of the T lymphocytes, which become specific for the presented bacteria, helping as part of a barrier and activating the immediate immune response. But the most important part of innate defense against certain pathogens is the role of neutrophils; which normally constitute between 60 and 70% of the immune response, migrate rapidly through the bloodstream to the site of infection, this migration is mediated by various chemoattractants such as IL-8 and leukotrienes type B. Recognition and subsequent phagocytosis of the invading microorganism is given by the neutrophils through the recognition pattern receptors. In addition to diverse specific molecular that are in the same neutrophils before diverse situations; as is the case of calprotein, which is formed in the same neutrophil cytoplasm, inhibiting the growth of bacteria such as S. aureus (Christaki *et al.,* 2014; Phillips *et al.,* 2012).

Approach of a patient with neutropenia and fever

Considering acute lymphoblastic leukemia as the main cause of pediatric cancer worldwide with an approximate prevalence of 25% and 72% of leukemias, where patients with low risk stratification can have a survival of up to 90% , infections are still the main cause of mortality in these patients (Khunara *et al.,* 2015; O´Connor *et al.,* 2003). finding that up to 40.8% of the cases are related to the treatment being more common during the induction period of the treatment up to 48% of the cases (O´Connor *et al.,* 2003; Lewis *et al.,* 2011). Fever of unknown origin in oncological patients is the main cause of admission to an emergency department in up to 20% of cases, which in many cases can also be caused by the same tumor activity, cancers such as leukemia, histocytosis, lymphomas, among others, are called "pyogenic cancers" due to the activity that they can produce (Lewis *et al.,* 2011; Loizidou *et al.,* 2016) and in many cases can confuse the presence of fever secondary to tumor activity. That is why it is important to know several risk factors that can predict which patients will reach an infectious process. The clinical evaluation at admission in these patients is of the utmost importance; categorizing the patient according to the risk, detect possible foci of infection and know how to recognize the etiology of it. A guided clinical history is the first step for the doctor, knowing about the background of the underlying disease and the chemotherapy applied, predict the time of neutropenia in these patients (Paganini *et al.,* 2011).

The clinical examination must include an assessment of each of the parts and organs of the body where an infectious process can be caused (Paige, 2013):

- Respiratory system: assess ears, nose and throat in search of sinusitis or rhinosinusitus data. The presence of tachypnea or hypoxia could be indicative of a developing pneumonic process.
- Cardiovascular: assessment of cardiac sounds, whether murmur or gallop noises; as well as body temperatures and assessment of the pulses in the extremities could indicate data of a compensated or decompensated shock.
- Gastrointestinal: The presence of abdominal pain, with diarrhea or blood in the stools could be indicative of pictures of typhoid, neutropenic colitis or pseudomembranous colitis
- Neurological. It is one of the most important evaluations that should be performed on the patient because, in addition to indicating a possible infectious focus, finding a patient with alterations in alertness could be indicative of a decompensated shock.

As well as assessment of oral manifestations that may be present in up to 40% of patients due to an inhibition of growth factors by the same chemotherapy and can be divided according to the classification of the World Health Organization for mucositis in 3 degrees (Paganini and Santolaya, 2011; Velten *et al.,* 2016):

- Grade 1 or incipient. Bright red oral mucosa with possible whitish areas. Continuous spontaneous pain is described
- Grade 2 or moderate. Localized ulcers are added, the child resists eating due to pain
- Grade 3 or serious. There is intense erythema and ulcerations or whitish areas. The great pain prevents the patient from eating and drinking, including swallowing saliva.

However, these concepts are very nonspecific to know if the patient is complicated or not, so it is important to know how to diagnose when we are facing a systemic inflammatory response picture. That is why there are different criteria to be able to diagnose it, which must be 2 or more of the following ones associated to distemperies or abnormalities in the leukocyte count (Randolph *et al.,* 2014):

- Alterations in heart rate: defined as tachycardia that is above two standard deviations (SD) for the patient's age; that is not modified by external stimuli, drugs or pain. Or bradycardia defined as that lower than the 10th percentile for the patient's age.
- Tachypnea, more than 2DS for the patient's age
- Alterations in body temperature. Defined as either the presence of fever (> 38.5ºC) or hypothermia (<36ºC)
- Alterations in the leukocyte account.

The importance of knowing the aforementioned criteria as part of a Systemic Inflammatory Response (SRIS) lies in the complex pathophysiology that responds to a case of infection, trauma, burns or other alterations (Balk, 2014). Leaving this as part of an early diagnosis of a possible complication such as sepsis and septic shock in the patient, which is the result of an increase in the diffusion of oxygen with a heterogeneous microcirculation during episodes of hypoperfusion with subsequent cell damage and increases in lactate and NADH in people (De Backer *et al.,* 2014). However, as we have said before; Due to the limited inflammatory reaction that these patients present, fever may be the only clinical manifestation of a serious infection (Bloos and Reinhart, 2014).

Laboratory studies

Upon admission, all patients should have the following complementary studies (Paganini and Santolaya, 2011).

- Hematic Biometry: As part of the protocol the importance lies in the diagnosis and classification of a neutropenia picture.
- Renal function tests.
- Liver function tests.
- Acute phase reactants. Several biomarkers as part of the study protocol in the face of an infectious process that in many cases are of importance in the face of an early process of sepsis among those found.
- C-reactive protein (CRP): which is released from the liver by stimulation of Interleukin-6 (IL-6). Having proinflammatory and anti-inflammatory function. Its secretion begins 4 to 6 hours after stimulation with a peak at 36 hours after the start of an infectious process (Bloos and Reinhart, 2014).
- Procalcitonin: It is a prohormone of calcitonin which is normally produced by the C cells of the thyroid glands; which in healthy people have levels of up to 0-1ng / ml (Bloos and Reinhart, 2014; Procalcitonin guided antibiotic therapy, 2012). Several markers have been compared with procalcitonia which recommend that it is within the main ones according to the acute phase reactants. In bacterial infections including sepsis procalcitonin levels are primarily found at values above 0.5 ng / ml.

As these are several acute phase reactants that support the diagnosis of an infectious process in these patients, however, the sensitivity and specificity will depend on the time of onset of symptoms and consecutively on the patient's clinical status, as could be done in studies performed by Bloos and Reinhart, in 2014 the most sensitive and specific are interleukin 6 with a sensitivity of 82% and specificity of 75%, compared to those previously discussed with C-reactive protein with sensitivity of 75% and specificity of 67% and procalcitonin of 77% and 79% respectively (Bloos and Reinhart, 2014).

Patient's status with neutropenia and fever

Part of the evaluation of patients during a process of neutropenia and fever; is the categorization of the risk of admission, which through various diagnostic scales and the use of complementary studies is to complement its diagnostic protocol to categorize it before the risk of presenting bacteremia and later a sepsis. These categorization scales will also help us to have a broader and more specific view about the type of treatment that will be used. Studies carried out in the pediatric oncology department in Buenos Aires, Argentina; where more than 500 episodes of neutropenia and fever were included in a period from 2006 to 2008, it was evident that factors such as the demographic status of the patients are not influential in the presence of an infection, however; it was found that acute lymphoblastic leukemia is one of the malignant diseases that are commonly associated with the presence of an infection during the induction phase of treatment; as well as a neutrophil count below 100cel / mm at the time of the feverish peak; among others, presenting a mortality rate of approximately 2% in most cases (Paganini *et al.,* 2011).

Table A. Factors of high risk of invasive bacterial infection, sepsis and / or mortality in children with cancer, neutropenia and fever (Santoloaya, 2011)

Age older 12 years
Type of cancer: leukemia, disease on the basis of induction, relapse or second tumor
Prediction of duration of neutropenia greater than 7 days
Fever. Axillary temperature> 39ºC
Clinical signs of sepsis
Ventilatory or intestinal involvement
Associated cormobility
RAN <100 cells / mm3
RAM <100 céls. / mm3
Platelet count <100 cells / mm3
Serum C-reactive protein> 90 mg / L
Interleukin-8> 300 pg / ml
Presence of bacteremia

These concepts vary from one hospital care center to another; studies carried out by Delebarrea and collaborators, in 2016 in hospitals in France; where from the concept of neutropenia and fever varies from one study to another, including the time of onset of symptoms influence the decision of the most appropriate antibiotic scheme for patients; factors such as the

type of cancer, the age of the patient, the onset of neutropenia among others are the most considered for the type of initial antimicrobial treatment (Delebarre *et al.,* 2016). Other rating systems are the MASCC (Multinational Association for Suportive Care in Cancer); which is mainly used in adults but which is also considered in the IDSA (Infectious Diseases Societyof America) Treatment Guidelines is another scale used to predict the risk of complications from bacteremia in these patients, up to 18% of cases with a mortality of 3%. The MASCC scale is a summary of the various risk factors that patients present at the time of febrile peak, so it has been seen that a MASCC score <15 points tend to present complications in 79% of cases (Klastersky *et al.,* 2014). However, the limitations in pediatric patients of this scoring system is related to the fact that it is mainly applied to adults, among other points to consider the presence of symptoms, with data on hypotension, obstructive pulmonary alterations, dehydration between others.

Table B. Multinational Association for Supportive Care in Cancer Risk-Index Score (MASCC)

Characteristic	Score
Presentation of febrile neutropenia with symptoms	5
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid or hematologic tumor without previous fungal infection	4
No dehydration	3
Presentation of febrile neutropenia with moderate symptoms	3
External patient	3

In conclusion; the categorization of risk at the beginning of a process of febrile neutropenia, regardless of the diagnostics caleused; previously said the recommendation of the use of the factors recommended by the Latin American guidelines for pediatric patients, will help us with the type of treatment to be used, being a very important tool to reduce antimicrobial resistance in the future as well as the days of treatment to follow and if the patient requires or not intrahospita lmanagement.

Treatment

The treatment of an oncological patient in the face of a process of febrile neutropenia must be somewhat aggressive, although it is true that most of the guidelines recommend that the treatment be to a certain extent specific for the etiologic agents mostly involved; recommendations have been made in recent years according to the agents most commonly found worldwide. Therefore, the treatment should be broad spectrum and bactericidal in a fast way, since infections in this type of host can progress rapidly causing the death of patients.

This case we will follow the recommendations for the initial empirical antibiotic treatment according to the guidelines on which the following work will be based; so we will take into account the guidelines of Diagnosis and treatment of febrile neutropenia in children with cancer of the Consensus of the Latin American Society of Pediatric Infectious Diseases.

Before starting a directed treatment, it´s necessary to categorize the patient, and to know which patients will be able to receive intra hospital or outpatient management, this according to the characteristics mentioned in previous sections, where the patient is categorized at the risk of a rapid progression of bacteremia and subsequently reaching a septic shock and death. All patients categorized as high risk should be hospitalized and receive intravenous treatment, in this case there are two treatment options, where antibiotic management will be directed primarily to Gram-negative agents, and with anti-pseudomonadic action.

Monotherapy: Third- or fourth-generation cephalosporins with antipseudomonic action (ceftazidime and cefepime), carbapenems (imipenemormeropenem) and antipseudomonias penicillins (piperaziline / tazobactamorticarcillin / clavulanicacid) have been equally effective for the treatment of febrile neutropenia and either alone or in combination with aminoglycosides (1). In comparison with other guidelines there are also recommendations to add another antibiotic to the initial management, other antibiotics (aminoglycosides, fluoroquinolones, and / orvancomycin) should be added to certain complications, whether the persistence of hypotension or suspected pneumonia

Other recommendations taken from different guidelines tell us to add certain types of antibiotics when there is documentation that the patient has had a previous infection with specific etiological agents multidrug-resistant or these have a high endemicity in hospital. For example

- Methicillin-resistant Staphylococcus aureus add vancomycin, linezolid or daptomycin
- Vancomycin resistant enterococci, add linezolid or daptomycin.
- Gram-negative bacteria that produce extended-spectrum Becta-lactamases, add carbapenemic
- Klebsiella pneumoniae resistant to carbapenemic add polymyxin-colistin.

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